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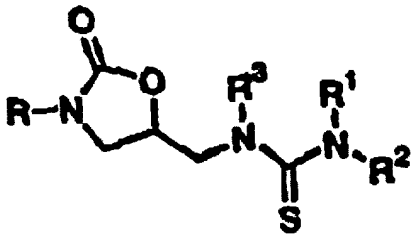
International patent search publication

(54) Title: THIOUREA DERIVATIVES

(54) Title: THIOUREA DERIVATIVES

(57) Abstract

Antimicrobial thiourea derivatives of general formula (I) or salts thereof: (wherein R^1, R^2, and R^3 are each hydrogen, alkyl, cycloalkyl, nitrogen-protecting group, alkoxycarbonylalkyl or the like; and R is phenyl which may be substituted by halogeno, hydroxyl, mercapto, amino, cyano, nitro, carboxyl, carbamoyl, alkyl, cycloalkyl, alkoxyl, alkylamino, alkanoyl, arylcarbonyl, aryl, aralkyl, aryloxy, cycloalkyloxy containing a heteroatom as a ring atom, a saturated heterocyclic group or the like).



(I)

USSN: 09/736,858 Filed: 12/14/2000 Art Unit: 1624
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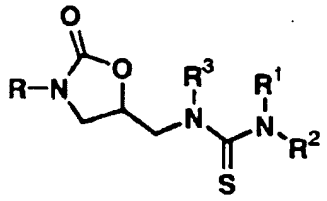
(57) Abstract

(I): Antimicrobial thiourea derivatives and salts thereof represented by general formula (I) below:



(R^1, R^2 and R^3 denote a hydrogen atom, alkyl group, cycloalkyl group, nitrogen atom protective group or alkoxycarbonylalkyl group, and R denotes a phenyl group or a phenyl group having the following substituent: halogen atom, hydroxyl group, mercapto group, amino group, cyano group, nitro group, carboxyl group, carbamoyl group, alkyl group, cycloalkyl group, alkoxy group, alkylamino group, alkanoyl group, arylcarbonyl group, aryl group, aralkyl group, aryloxy group, cycloalkyloxy group having a heteroatom as a ring constitutive atoms or saturated heterocyclic group).

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SPECIFICATION

THIOUREA DERIVATIVES

Technological Field

The present invention relates to novel thiourea derivatives and salts thereof that are useful as antimicrobial agents.

Background Art

N-[(3-aryl-2-oxooxazolidine-5-yl)methyl]acetamide derivative are disclosed in Japanese Unexamined Patent Application No. 60-8277 and in the *Journal of Medicinal Chemistry* 39, 673 (1996); 3-aryl-5-hydroxymethyl-2-oxooxazolidine derivatives, 3-aryl-5-halogenomethyl2-oxooxazolidine derivatives and other compounds are disclosed in *Current Pharmaceutical Design* 2, 175 (1996) and the *Journal of Medicinal Chemistry* 32, 1673 (1989); and N-(3-heteroaryl-2-oxooxazolidine-5-yl)methylthioacetamide derivatives and N-(3-heteroaryl-2-oxooxazolidine-5-yl)methyl-N'-methylthiourea derivatives and other compounds are disclosed in Japanese Unexamined Patent Application No. Hei 9-316073 as compounds having 3-aryl-2-oxooxazolidine backbones. These compounds are referred to as oxazolidinone antibiotics and are known to have antimicrobial activity with respect to Gram-positive bacteria (Hayakawa, I., *Fine Chemical* 27(1), 37-45 (1998)). However, the antimicrobial activity of these compounds is not yet sufficient, and the development of improved antimicrobial agents is desired.

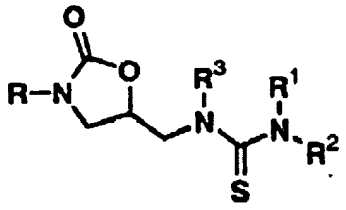
Disclosure of the invention

Various types of antimicrobial agents such as antibiotics and synthetic antimicrobial agents having different mechanisms of action have been offered for clinical use as therapeutic agents for diseases. However, in using these antimicrobial agents, problems have arisen on a global scale with the appearance of multidrug-resistant bacteria typified by bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA). The object of the present invention is to offer a compound having excellent antimicrobial activity

with respect to clinically isolated strains which include standard microorganisms and multidrug resistant microorganisms

The inventors of the present invention et al., as a result of painstaking research towards a solution to the above problems, discovered that novel thiourea derivatives and salts thereof represented by the general formula below have superior antimicrobial activity with respect to clinically isolated bacteria including multidrug-resistant microorganisms as well as standard microorganisms, and thus arrived at the present invention.

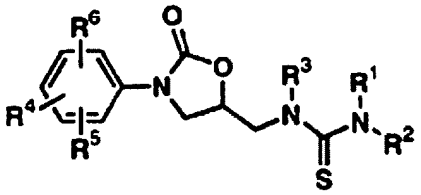
Specifically, the present invention offers thiourea derivatives and salts thereof represented by general formula (I) below:



(I)

(in the formula, R^1, R^2 and R^3 each denotes a hydrogen atom, alkyl group, cycloalkyl group, nitrogen atom protective group, alkoxycarbonylalkyl group, substitutable amino group, substitutable aryl group or substitutable benzyl group; and R denotes a substitutable phenyl group).

In a preferred mode of the above invention, the present invention offers thiourea derivatives or salts thereof represented by general formula (II) below:



(II)

(in the formula, R^1, R^2 and R^3 each denotes a hydrogen atom, alkyl group, cycloalkyl group, nitrogen atom protective group, alkoxycarbonylalkyl group, substitutable amino group, substitutable aryl group or substitutable benzyl group; R^4, R^5 and R^6 each individually denotes a hydrogen atom, halogen atom, hydroxyl group, mercapto group, amino group, cyano group, nitro group, carboxyl group, carbamoyl group, substitutable alkyl group, substitutable cycloalkyl group, substitutable alkenyl group, substitutable alkynyl group, substitutable alkoxy group, substitutable alkylthio group, substitutable

alkylamino group, substitutable dialkylamino group, substitutable alkylaminocarbonyl group, substitutable dialkylaminocarbonyl group, substitutable alkanoyl group, substitutable halogenoalkanoyl group, substitutable alkanesulfonyl group, substitutable arylcarbonyl group, substitutable aryl group, substitutable aralkyl group, substitutable aryloxy group, substitutable cycloalkyloxy group containing heteroatoms as ring constitutive atoms or substitutable saturated heterocyclic groups; or any two groups of R^4, R^5 and R^6 may form, together with a benzene ring, substitutable hydrocarbon condensed rings).

In another aspect, the present invention offers drugs that contain the aforementioned thiourea derivatives or salts thereof as effective components. Drugs that are offered by the present invention can be appropriately used, for example, as antimicrobial agents. In an additional aspect, the present invention offers use of the aforementioned thiourea derivatives or salts thereof in the manufacture of the above drugs; and a method for treating infections involving a process for administering therapeutically effective amounts of the aforementioned thiourea derivatives or salts thereof to mammals including humans.

Best Mode for Carrying Out the Invention

A detailed description will be presented regarding the compounds of general formula (II) above which is a preferred mode of the thiourea derivatives of the present invention. The compounds are characterized in that R in the thiourea derivatives represented by general formula (I) are specific substituted phenyl groups or unsubstituted phenyl groups. Moreover, the scope of the present invention is not restricted to the compounds of general formula (II) above, as the compounds represented by general formula (I) (compounds wherein R is a substituted or unsubstituted phenyl group) are all within the scope of the present invention.

The alkyl groups represented by R^1, R^2, R^3, R^4, R^5 and R^6 are linear or branched alkyl groups with carbon numbers of 1-6, and examples that may be cited include methyl groups, ethyl groups, n-propyl groups, isopropyl groups, n-butyl groups, isobutyl groups, sec-butyl groups, tert-butyl groups, n-pentyl groups, isopentyl groups, neopentyl groups and n-hexyl groups, and the cycloalkyl groups are cycloalkyl groups with carbon

numbers of 3-6, where examples that may be cited include cyclopropyl groups, cyclobutyl groups, cyclopentyl groups and cyclohexyl groups. In this specification, the term "cycloalkyl groups" is a general term that includes alkyl groups having cycloalkyl moieties (e.g., a cyclopropylmethyl group). Examples of aryl groups that may be cited are monocyclic and polycyclic aromatic groups such as a phenyl group, pyridin-2-yl group, pyridin-3-yl group, pyridin-4-yl group, pyrazin-2-yl group, pyrazin-3-yl group, pyrimidin-2-yl group, pyrimidin-4-yl group, furan-2-yl group, furan-3-yl group, thiophen-2-yl group, thiophen-3-yl group, naphthalen-1-yl group, naphthalene-2-yl group, benzofuran-4-yl group, benzofuran-5-yl group, benzofuran-6-yl group, benzofuran-7-yl group, benzo[b]thiophen-4-yl group, benzo[b]thiophen-5-yl group, benzo[b]thiophen-6-yl group and benzo[b]thiophen-7-yl group.

In addition, the nitrogen atom protective groups represented by R^1, R^2 and R^3 may be any group that is substantially inert in systems in which the nitrogen atoms are not to participate in the reaction, and in addition, which readily dissociate under specific deprotective reaction conditions. Examples of protective groups that may be cited include alkanoyl groups, halogenoalkanoyl groups, arylcarbonyl groups, aryloxycarbonyl groups aralkyloxycarbonyl groups and alkoxycarbonyl groups. More specifically, examples of alkanoyl groups that may be cited include formyl groups, acetyl groups, propionyl groups, butyryl groups and pivaloyl groups. Examples of halogenoalkanoyl groups are any groups wherein one or two of the same or different halogen atoms are substituted on the above alkanoyl groups, where the halogen atom is a fluorine atom, chlorine atom, bromine atom or iodine atom. Examples that may be cited include a fluoroacetyl group, difluoroacetyl group, trifluoracetyl group, chloroacetyl group, dichloroacetyl group, and trichloroacetyl group. In addition, examples of arylcarbonyl groups that may be cited include a benzoyl group, 4-phenylbenzoyl group, 4-methoxybenzoyl group, 2-nitrobenzoyl group and 2-(benzoyloxymethyl)benzoyl group. Examples of aryloxycarbonyl groups that may be cited include a phenyloxycarbonyl group and 2,4,6-tri-n-butylphenyloxycarbonyl group. Examples of aralkyloxycarbonyl groups that may be cited include a benzoyloxycarbonyl group, 4-methoxybenzyloxycarbonyl group, 4-bromobenzyloxycarbonyl group and 2,4,6-trimethylbenzyloxycarbonyl group. Examples of alkoxycarbonyl groups that may

be cited include a methoxycarbonyl group, ethoxycarbonyl group, n-propoxycarbonyl and tert-butoxycarbonyl group.

Examples of alkoxycarbonylalkyl groups represented by R^1, R^2 and R^3 that may be cited include a methoxycarbonylethyl group, ethoxycarbonylethyl group, n-propoxycarbonyl ethyl group, isopropoxycarbonylethyl group, n-butoxycarbonylethyl group, sec-butoxycarbonylethyl group, tert-butoxycarbonylethyl group, methoxycarbonylpropyl group, ethoxycarbonylpropyl group, n-propoxycarbonylpropyl group, isopropoxycarbonylpropyl group, n-butoxycarbonylpropyl group, sec-butoxycarbonylpropyl group, tert-butoxycarbonylpropyl group and ethoxycarbonylbutyl group.

Halogen atoms represented by R^4, R^5 and R^6 in general formula (II) above that may be used are a fluorine atom, chlorine atom, bromine atom and iodine atom. Examples of alkenyl groups that may be used are alkenyl groups with carbon numbers of 2-4, and specific examples that may be cited include a vinyl group, propenyl group and butenyl group. Examples of alkynyl groups that may be used are alkynyl groups with carbon numbers of 2-4, and specific examples that may be cited include an ethynyl group, propynyl group and butynyl group. In addition, examples of the alkoxy group represented by R^4, R^5 and R^6 that may be cited include a methoxy group, ethoxy group, n-propoxy group, isopropoxy group, n-butoxy group, isobutoxy group, sec-butoxy group, tert-butoxy group, n-pentyloxy group, isopentyloxy group, neopentyloxy group and n-hexyloxy group. Examples of alkylthio groups that may be cited include a methylthio group, ethylthio group, n-propylthio group, isopropylthio group, n-butylthio group, isobutylthio group, sec-butylthio group, tert-butylthio group, n-pentylthio group, isopentylthio group, neopentylthio group and n-hexylthio group.

Examples of alkylamino groups or dialkylamino groups expressed by R^4, R^5 and R^6 that may be used are amino groups substituted with linear or cyclic alkyl groups having carbon numbers of 1-6. More specific examples that may be cited include a methylamino group, ethylamino group, n-propylamino group, isopropylamino group, n-butylamino group, isobutylamino group, sec-butylamino group, tert-butylamino group, n-pentylamino group, isopentylamino group, neopentylamino group, n-hexylamino group, dimethylamino group, diethylamino group, N-ethyl-N-methylamino group,

N-methyl-N-n-propylamino group, N-isopropyl-N-methylamino group, N-n-butyl-N-methylamino group, N-isobutyl-N-methylamino group, N-sec-butyl-N-methylamino group, N-tert-butyl-N-methylamino group, N-methyl-N-n-pentylamino group, N-isopentyl-N-methylamino group, N-methyl-N-neopentylamino group, N-n-hexyl-N-methylamino group, cyclopropylamino group, cyclobutylamino group, cyclopentylamino group, cyclohexylamino group, N-cyclopropyl-N-methylamino group, N-cyclobutyl-N-methylamino group, N-cyclopentyl-N-methylamino group and N-cyclohexyl-N-methylamino group.

In addition, examples of the alkylaminocarbonyl groups or dialkylaminocarbonyl groups represented by R^4, R^5 and R^6 that may be used are aminocarbonyl groups substituted with linear or cyclic alkyl groups with carbon numbers of 1-6. More specific examples that may be cited include a methylaminocarbonyl group, ethylaminocarbonyl group, n -propylaminocarbonyl group, isopropylaminocarbonyl group, n-butylaminocarbonyl group, isobutylaminocarbonyl group, sec-butylaminocarbonyl group, tert-butylaminocarbonyl group, n-pentylaminocarbonyl group, isopentylaminocarbonyl group, neopentylaminocarbonyl group, n-hexylaminocarbonyl group, dimethylaminocarbonyl group, diethylaminocarbonyl group, N-ethyl-N-methylaminocarbonyl group, N-methyl-N-n-propylaminocarbonyl group, N-isopropyl-N-methylaminocarbonyl group, N-n-butyl-N-methylaminocarbonyl group, N-isobutyl-N-methylaminocarbonyl group, N-sec-butyl-N-methylaminocarbonyl group, N-tert-butyl-N-methylaminocarbonyl group, N-methyl-N-n-pentylaminocarbonyl group, N-isopentyl-N-methylaminocarbonyl group, N-methyl-N-neopentylaminocarbonyl group, N-n-hexyl-N-methylaminocarbonyl group, cyclopropylaminocarbonyl group, cyclobutylaminocarbonyl group, cyclopentylaminocarbonyl group, cyclohexylaminocarbonyl group, N-cyclopropyl-N-methylaminocarbonyl group, N-cyclobutyl-N-methylaminocarbonyl group, N-cyclopentyl-N-methylaminocarbonyl group or N-cyclohexyl-N-methylaminocarbonyl group.

Examples of alkanoyl groups represented by R^4, R^5 and R^6 that may be cited include an acetyl group, propionyl group, butyryl group, isobutyryl group, valeryl group, isovaleryl group, hexanoyl group and heptanoyl group. Examples of halogenoalkanoyl groups that may be used are groups wherein one or more of the same or different halogen

atoms are substituted on the aforementioned alkanoyl groups, where halogen atoms that may be used are fluorine atoms, chlorine atoms, bromine atoms and iodine atoms. Examples that may be cited include a fluoroacetyl group, difluoroacetyl group, trifluoroacetyl group, chloroacetyl group, dichloroacetyl group and trichloroacetyl group. Examples of alkanesulfonyl groups that may be used are linear or branched alkyl-substituted sulfonyl groups with carbon numbers of 1-6, and more specific examples that may be cited include a methanesulfonyl group, ethanesulfonyl group, n-propanesulfonyl group, isopropanesulfonyl group and n-butanesulfonyl group. Examples of arylcarbonyl groups that may be cited include a benzoyl group, 4-phenylbenzoyl group, 4-methoxybenzoyl group, 2-nitrobenzoyl group and 2-(benzoyloxymethyl)benzoyl group. Examples of aralkyl groups that may be used are alkyl groups with carbon numbers of 1-4 that have been substituted with aryl groups, and more specific examples that may be cited include a benzyl group, phenethyl group, phenylpropyl group, phenylbutyl group, (pyridine-2-yl)methyl group, (pyridine-3-yl)methyl group and (pyridine-4-yl)methyl group. Examples of aryloxy groups that may be cited include a phenyloxy group, pyridinyloxy group, pyrimidinyloxy group, pyrazinyloxy group, furyloxy group and thienyloxy group.

Examples of cycloalkyloxy groups that contain heteroatoms as ring constituent atoms that may be cited include an acetidinyloxy group, pyrrolidinyloxy group, piperidinyloxy group, homopiperidinyloxy group, oxetanyloxy group, tetrahydrofuranyloxy group, tetrahydropyranyloxy group, thietanyloxy group, tetrahydrothiophenyloxy group, tetrhaydrothiopyranyloxy group, oxazolidinyloxy group ,thiazolidinyloxy group, piperazinyloxy group, morpholinyloxy group, thiomorpholinyloxy group, 1-oxido-4-thiomorpholinyloxy group, 1,1-dioxido-4-thiomorpholinyloxy group, homopiperidyloxy group, 3-azabicyclo[3.3.0]octanyloxy group and 3,7-diazabicyclo[3.3.0]octanyloxy group. Examples of saturated heterocyclic groups that may be cited include an azetidinyl group, pyrrolidinyl group, oxazolidinyl group, thiazolidinyl group, piperidyl group, piperazinyl group, oxetanyl group, tetrahydrofuranyl group, tetrahydropyranyl group, thietanyl group, tetrahydrothiophenyl group, tetrahydrothiopyranyl group, morpholinyl group, thiomorpholinyl group, 1-oxido-4-thiomorpholinyl group, 1,1-dioxido-4-

thiomorpholinyl group, homopiperidyl group, homopiperazinyl group, 3-azabicyclo[3.3.0]octanyl group and 3,7-diazabicyclo[3.3.0]octanyl group.

Examples of groups produced when any two of R^4, R^5 and R^6 form a hydrocarbon condensed ring together with a benzene ring that may be cited include an indan-5-yl group, 1-indanon-5-yl group, inden-5-yl group, inden-6-yl group, 1-indanon-6-yl group, 2-indanon-5-yl group, 1,3-indandion-5-yl group, naphthalene-2-yl group, 1(2H)-naphthalenon-6-yl group, 1(2H)-naphthalenon-7-yl group, 1,2,3,4-tetrahydronaphthalen-6-yl group, 1,2,3,4-tetrahydro-1-naphthalenon-6-yl group, 1,2,3,4-tetrahydro-1-naphthalenon-7-yl group, 1,2,3,4-tetrahydro-2-naphthalenon-6-yl group, 1,2,3,4-tetrahydro-2-naphthalenon-7-yl group, 1,2-naphthoquinon-6-yl group, 1,2-naphthoquinon-7-yl group, 1,4-naphthoquinon-6-yl group, fluoren-2-yl group, fluoren-3-yl group, fluorenon-2-yl group, fluorenon-3-yl group, anthracen-2-yl group and anthracen-3-yl group.

In this specification, the term "substitutable" in reference to functional groups has no particular restrictions on the number or type of substituent, and when two or more substituents are present, they may be the same or different. Examples of these types of substituents that may be cited include an alkyl group, cycloalkyl group, hydroxyl group, mercapto group, alkoxy group, alkylthio group, halogen atom, amino group, alkylamino group, dialkylamino group, cyano group, nitro group, alkoxyalkyl group, alkoxycarbonylalkyl group, carboxyalkyl group, hydroxyalkanoyl group, alkoxyalkoxy group, alkoxyalkanoyl group, benzyloxycarbonyl group, benzyloxyalkanoyl group, alkylaminoalkoxy group, dialkylaminoalkoxy group, alkylaminoalkyl group, dialkylaminoalkyl group, halogenoalkyl group, oxo group, alkyloxyimino group, aryloxyimino group, carboxyl group, alkylcarbonyl group, alkylcarbonylalkyl group, carbamoyl group, aryl group or aralkyl group.

Examples of the substituted phenyl group represented by R in the thiourea derivatives of the present invention that may be cited include a 4-methylphenyl group, 3-methylphenyl group, 2-methylphenyl group, 3,4-dimethylphenyl group, 3,5-dimethylphenyl group, 4-ethylphenyl group, 4-n-propylphenyl group, 4-isopropylphenyl group, 4-n-butylphenyl group, 4-isobutylphenyl group, 4-n-pentylphenyl group, 4-isopentylphenyl group, 4-n-hexylphenyl group,

4-cyclopropylphenyl group, 4-cyclobutylphenyl group, 4-cyclopentylphenyl group, 4-cyclohexylphenyl group, 4-methoxyphenyl group, 3-methoxyphenyl group, 3,4-dimethoxyphenyl group, 3,5-dimethoxyphenyl group, 4-ethoxyphenyl group, 4-n-propoxyphenyl group, 4-isopropoxyphenyl group, 4-n-butoxyphenyl group, 4-isobutoxyphenyl group, 4-n-pentyloxyphenyl group, 4-isopentyloxyphenyl group, 4-n-hexyloxyphenyl group, 4-methylaminophenyl group, 3-methylaminophenyl group, 4-ethylaminophenyl group, 4-n-propylaminophenyl group, 4-isopropylaminophenyl group, 4-n-butylaminophenyl group, 4-isobutylaminophenyl group, 4-n-pentylaminophenyl group, 4-isopentylaminophenyl group, 4-n-hexylaminophenyl group, 4-dimethylaminophenyl group, 4-(N-ethyl)-N-methylamino)phenyl group, 4-(N-methyl-N-n-propylamino)phenyl group, 4-(N-isopropyl-N-methylamino)phenyl group, 4-(N-n-butyl-N-methylamino)phenyl group, 4-(N-isobutyl-N-methylamino)phenyl group, 4-(N-methyl-N-n-pentylamino)phenyl group, 4-(N-isopentyl-N-methylamino)phenyl group, 4-(N-n-hexyl-N-methylamino)phenyl group, 4-[(2-dimethylaminoethyl)amino]phenyl group, 4-[(2-dimethylaminoethyl)amino]-3-fluorophenyl group, 4-[(2-dimethylaminoethyl)amino]-3,5-difluorophenyl group, 4-[N-(2-dimethylaminoethyl)-N-methylamino]phenyl group, 4-[N-(2-dimethylaminoethyl)-N-methylamino]-3-fluorophenyl group, 4-[N-(2-dimethylaminoethyl)-N-methylamino]-3,5-difluorophenyl group, 4-[(2-diethylaminoethyl)amino]phenyl group, 4-[(2-diethylaminoethyl)amino]-3-fluorophenyl group, 4-[(2-diethylaminoethyl)amino]-3,5-difluorophenyl group, 4-[N-(2-diethielaminoethyl)-N-methylamino]phenyl group [sic; possibly "4-[N-(2-diethynylaminoethyl)-N-methylamino]phenyl group"] , 4-[N-(2-diethyldiethielaminoethyl)-N-methylamino]-3-fluorophenyl group [sic; possibly "4-[N-(2-diethyldiethynylaminoethyl)-N-methylamino]-3-fluorophenyl group"], 4-[N-(2-diethielaminoethyl)-N-methylamino]-3,5-difluorophenyl group [sic; possibly "4-[N-(2-diethielaminoethyl)-N-methylamino]-3,5-difluorophenyl group"], 4-cyclopropylaminophenyl group, 4-cyclobutylaminophenyl group, 4-cyclopentylaminophenyl group, 4-cyclohexylaminophenyl group, 4-acetylphenyl group, 4-acetyl-3-fluorophenyl group, 4-propionylphenyl group, 3-fluoro-4-propionylphenyl group, 4-butyrylphenyl group, 4-butyryl-3-fluorophenyl group, 4-isobutyrylphenyl group, 3-fluoro-4-isobutyrylphenyl group, 4-valerylphenyl group,

3-fluoro-4-valerylphenyl group, 4-(2-dimethylaminoethoxy)phenyl group, 4-(hydroxymethyl)phenyl group, 4-(1-hydroxyethyl)phenyl group, 4-hydroxyethyl)phenyl group, 4-(2-dimethylaminoethoxy)-3-fluorophenyl group, 4-(3-dimethylaminopropoxy)phenyl group, 4-(3-dimethylaminopropoxy)-3-fluorophenyl group, 4-(4-dimethylaminobutoxy)phenyl group, 4-(4-dimethylaminobutoxy)-3-fluorophenyl group, 4-(2-methoxyethoxy)phenyl group, 3-fluoro-4-(2-methoxyethoxy)phenyl group, 4-(azetidin-1-yl)phenyl group, 4-(azetidin-1-yl)-3-fluorophenyl group, 4-(azetidin-1-yl)-3,5-difluorophenyl group, 4-(3-hydroxyazetidin-1-yl)phenyl group, 3-fluoro-4-(3-hydroxyazetidin-1-yl)phenyl group, 3,5-difluoro-4-(3-hydroxyazetidin-1-yl)phenyl group, 4-(3-oxoazetidin-1-yl)phenyl group, 3-fluoro-4-(3-oxoazetidin-1-yl)phenyl group, 3,5-difluoro-4-(3-oxoazetidin-1-yl)phenyl group, 4-(3-methoxyazetidin-1-yl)phenyl group, 3-fluoro-4-(3-methoxyazetidin-1-yl)phenyl group, 3,5-difluoro-4-(3-methoxyazetidin-1-yl)phenyl group, 4-[3-(2-methoxyethoxy)azetidin-1-yl]phenyl group, 3-fluoro-4-[3-(2-methoxyethoxy)azetidin-1-yl]phenyl group, 3,5-difluoro-4-[3-(2-methoxyethoxy)azetidin-1-yl]phenyl group, 4-(3-aminoazetidin-1-yl)phenyl group, 4-(3-aminoazetidin-1-yl)-3-fluorophenyl group, 4-(3-aminoazetidin-1-yl)-3,5-difluorophenyl group, 4-(3-dimethylaminoazetidin-1-yl)phenyl group, 4-(3-dimethylaminoazetidin-1-yl)-3-fluorophenyl group, 4-(3-dimethylaminoazetidin-1-yl)-3,5-difluorophenyl group, 4-(pyrrolidin-1-yl)phenyl group, 3-fluoro-4-(pyrrolidin-1-yl)phenyl group, 3,5-difluoro-4-(pyrrolidin-1-yl)phenyl group, 4-(3-hydroxypyrrolidin-1-yl)phenyl group, 3-fluoro-4-(3-hydroxypyrrolidin-1-yl)phenyl group, 3,5-difluoro-4-(3-hydroxypyrrolidin-1-yl)phenyl group, 4-(3-oxopyrrolidin-1-yl)phenyl group, 3-fluoro-4-(3-oxopyrrolidin-1-yl)phenyl group, 3,5-difluoro-4-(3-oxopyrrolidin-1-yl)phenyl group, 4-(3-methoxypyrrolidin-1-yl)phenyl group, 3-fluoro-4-(3-methoxypyrrolidin-1-yl)phenyl group, 3,5-difluoro-4-(3-methoxypyrrolidin-1-yl)phenyl group, 4[3-(2-methoxyethoxy)pyrrolidin-1-yl]phenyl group, 3-fluoro-4-[3-(2-methoxyethoxy)pyrrolidin-1-yl]phenyl group, 3,5-difluoro-4-[3-(2-methoxyethoxy)pyrrolidin-1-yl]phenyl group, 4-(3-aminopyrrolidin-1-yl)phenyl group, 4-(3-aminopyrrolidin-1-yl)-3-fluorophenyl group, 4-(3-aminopyrrolidin-1-yl)-3,5-difluorophenyl group, 4-(3-dimethylaminopyrrolidin-1-yl)phenyl group, 4-(3-dimethyaminopyrrolidin-1-yl)-3-fluorophenyl group, 4-(3-dimethylaminopyrrolidin-1-

yl)-3,5-difluorophenyl group, 4-(piperidine-1-yl)phenyl group, 3-fluoro-4-(piperidine-1-yl)phenyl group, 3,5-difluoro-4-(piperidine-1-yl)phenyl group, 4-(4-hydroxypiperidin-1-yl)phenyl group, 3-fluoro-4-(4-hydroxypiperidin-1-yl)phenyl group, 3,5-difluoro-4-(4-hydroxypiperidin-1-yl)phenyl group, 4-(4-oxopiperidin-1-yl)phenyl group, 3-fluoro-4-(4-oxopiperidin-1-yl)phenyl group, 3,5-difluoro-4-(4-oxopiperidin-1-yl)phenyl group, 4-(4-methoxypiperidin-1-yl)phenyl group, 3-fluoro-4-(4-methoxypiperidin-1-yl)phenyl group, 3,5-difluoro-4-(4-methoxypiperidin-1-yl)phenyl group, 4-[4-(2-methoxyethoxy)piperidin-1-yl]phenyl group, 3-fluoro-4-[4-(2-methoxyethoxy)piperidine-1-yl]phenyl group, 3,5-difluoro-4-[4-(2-methoxyethoxy)piperidine-1-yl]phenyl group, 4-(4-aminopiperidin-1-yl)phenyl group, 4-(4-aminopiperidin-1-yl)-3-fluorophenyl group, 4-(4-aminopiperidin-1-yl)-3,5-difluorophenyl group, 4-(4-dimethylaminopiperidin-1-yl)phenyl group, 4-(4-dimethylaminopiperidin-1-yl)-3-fluorophenyl group, 4-(4-dimethylaminopiperidin-1-yl)-3,5-difluorophenyl group, 4-(piperidine-1-yl)phenyl group, 3-fluoro-4-(piperidine-1-yl)phenyl group, 3,5-difluoro-4-(piperazin-1-yl)phenyl group, 4-(4-methylpiperazin-1-yl)phenyl group, 3-fluoro-4-(4-methylpiperazin-1-yl)phenyl group, 3,5-difluoro-4-(4-methylpiperazin-1-yl)phenyl group, 4-(4-ethylpiperazin-1-yl)phenyl group, 4-(4-ethylpiperazin-1-yl)-3-fluorophenyl group, 4-(4-ethylpiperazin-1-yl)-3,5-difluorophenyl group, 4-(4-n-propylpiperazin-1-yl)phenyl group, 3-fluoro-4-(4-n-propylpiperazin-1-yl)phenyl group, 3,5-difluoro-4-(4-n-propylpiperazin-1-yl)phenyl group, 4-(4-n-butylpiperazin-1-yl)phenyl group, 4-(4-n-butylpiperazin-1-yl)-3-fluorophenyl group, 4-(4-n-butylpiperazin-1-yl)-3,5-difluorophenyl group, 4-(4-hydroxyacetylpiperazin-1-yl)phenyl group, 3-fluoro-4-(4-hydroxyacetylpiperazin-1-yl)phenyl group, 3,5-difluoro-4-(4-hydroxyacetylpiperazin-1-yl)phenyl group, 4-(4-benzyloxyacetylpiperazin-1-yl)phenyl group, 4-(4-benzyloxyacetylpiperazin-1-yl)-3-fluorophenyl group, 4-(4-benzyloxyacetylpiperazin-1-yl)-3,5-difluorophenyl group, 4-[4-(3-methoxypropionyl)piperazin-1-yl]phenyl group, 3-fluoro-4-[4-(3-methoxypropionyl)piperazin-1-yl]phenyl group, 3,5-difluoro-4-[4-(3-methoxypropionyl)piperazin-1-yl]phenyl group, 4-[4-(3-ethoxypropionyl)piperazin-1-yl]phenyl group, 4-[4-(3-ethoxypropionyl)piperazin-1-yl]-3-fluorophenyl group, 4-[4-(3-ethoxypropionyl)piperazin-1-yl]-3,5-difluorophenyl group, 4-[4-(2-ethoxycarbonylethyl)piperazin-1-yl]phenyl group, 4-[4-(2-

ethoxycarbonylethyl)piperazin-1-yl]-3-fluorophenyl group, 4-[4-(2-ethoxycarbonylethyl)piperazin-1-yl]-3,5-difluorophenyl group, 4-[4-(2-methoxycarbonylethyl)piperazin-1-yl]phenyl group, 3-fluoro-4-[4-(2-methoxycarbonylethyl)piperazin-1-yl]phenyl group, 3,5-difluoro-4-[4-(2-methoxycarbonylethyl)piperazin-1-yl]phenyl group, 4-[4-(2-carboxyethyl)piperazin-1-yl]phenyl group, 4-[4-(2-carboxyethyl)piperazin-1-yl]-3-fluorophenyl group, 4-[4-(2-carboxyethyl)piperazin-1-yl]-3,5-difluorophenyl group 4-(4-benzyloxycarbonylpiperazin-1-yl)phenyl group, 4-(4-benzyloxycarbonylpiperazin-1-yl)-3-fluorophenyl group, 4-(4-benzyloxycarbonylpiperazin-1-yl)-3,5-difluorophenyl group, 4-(morpholin-4-yl)phenyl group, 3-fluoro-4-(morpholin-4-yl)phenyl group, 3,5-difluoro-4-(morpholin-4-yl)phenyl group, 4-(thiomorpholin-4-yl)phenyl group, 3-fluoro-4-(thiomorpholin-4-yl)phenyl group, 3,5-difluoro-4-(thiomorpholin-4-yl)phenyl group, 4-(1-oxidothiomorpholin-4-yl)phenyl group, 3-fluoro-4-(1-oxidothiomorpholin-4-yl)phenyl group, 3,5-difluoro-4-(1-oxidothiomorpholin-4-yl)phenyl group, 4-(1,1-dioxidothiomorpholin-4-yl)phenyl group, 4-(1,1-dioxidothiomorpholin-4-yl)-3-fluorophenyl group, 4-(1,1-dioxidothiomorpholin-4-yl)-3,5-difluorophenyl group, 3-methoxy-4-(morpholin-4-yl)phenyl group, 3-ethoxy-4-(morpholin-4-yl)phenyl group, 4-(morpholin-4-yl)-3-n-propoxyphenyl group, 3-(2-methoxyethoxy)-4-(morpholin-4-yl)phenyl group, 4-phenoxyphenyl group, 3-fluoro-4-phenoxyphenyl group, 3,5-difluoro-4-phenoxyphenyl group, 4-(pyridine-4-yl)oxyphenyl group, 3-fluoro-4-(pyridine-4-yl)oxyphenyl group, 3,5-difluoro-4-(pyridine-4-yl)oxyphenyl group, 4-(pyridine-3-yl)oxyphenyl group, 3-fluoro-4-(pyridine-3-yl)oxyphenyl group, 3,5-difluoro-4-(pyridine-3-yl)oxyphenyl group, 4-(pyridine-2-yl)oxyphenyl group, 3-fluoro-4-(pyridine-2-yl)oxyphenyl group, 3,5-difluoro-4-(pyridine-2-yl)oxyphenyl group, 4-(furan-2-yl)oxyphenyl group, 3-fluoro-4-(furan-2-yl)oxyphenyl group, 3,5-difluoro-4-(furan-2-yl)oxyphenyl group, 4-(furan-3-yl)oxyphenyl group, 3-fluoro-4-(furan-3-yl)oxyphenyl group, 3,5-difluoro-4-(furan-3-yl)oxyphenyl group, 4-(thiophen-2-yl)oxyphenyl group, 3-fluoro-4-(thiophen-2-yl)oxyphenyl group, 3,5-difluoro-4-(thiophen-2-yl)oxyphenyl group, 4-(thiophen-3-yl)oxyphenyl group, 3-fluoro-4-(thiophen-3-yl)oxyphenyl group, 3,5-difluoro-4-(thiophen-3-yl)oxyphenyl group, 4-[(N-methylazetidin-3-yl)oxy]phenyl group, 3-fluoro-4-[(N-methylazetidin-3-yl)oxy]phenyl group, 3,5-difluoro-4-[(N-methylazetidin-3-

yl)oxy]phenyl group, 4-[(N-ethylazetidin-3-yl)oxy]phenyl group, 4-[(N-ethylazetidin-3-yl)oxy]-3-fluorophenyl group, 4-[(N-ethylazetidin-3-yl)oxy[-3,5-difluorophenyl group, 4-[(N-n-propylazetidin-3-yl)oxy]phenyl group, 3-fluoro-4-[(N-n-propylazetidin-3-yl)oxy]phenyl group, 3,5-difluoro-4-[(N-n-propylazetidin-3-yl)oxy]phenyl group, 4-[(N-n-butylazetidin-3-yl)oxy]phenyl group, 4-[(N-n-butylazetidin-3-yl)oxy]-3-fluorophenyl group, 4-[(N-n-butylazetidin-3-yl)oxy]-3,5-difluorophenyl group, 4-[(N-hydroxyacetylazetidin-3-yl)oxy]phenyl group, 3-fluoro-4-[(N-hydroxyacetylazetidin-3-yl)oxy]phenyl group, 3,5-difluoro-4-[(N-hydroxyacetylazetidin-3-yl)oxy]phenyl group, 4-[[N-(3-methoxypropionyl)azetidin-3-yl]oxy]phenyl group, 3-fluoro-4-[[N-(3-methoxypropionyl)azetidin-3-yl]oxy]phenyl group, 3,5-difluoro-4-[[N-(3-methoxypropionyl)azetidin-3-yl]oxy]phenyl group, 4-[(N-methylpiperidin-4-yl)oxy]phenyl group, 3-fluoro-4-[(N-methylpiperidin-4-yl)oxy]phenyl group, 3,5-difluoro-4-[(N-methylpiperidin-4-yl)oxy]phenyl group, 4-[(N-ethylpiperidin-4-yl)oxy]phenyl group, 4-[(N-piperidin-4-yl)oxy]-3-fluorophenyl group, 4-[(N-ethylpiperidin-4-yl)oxy]-3,5-difluorophenyl group, 4-[(N-n-propylpiperidin-4-yl)oxy]phenyl group, 3-fluoro-4-[(N-n-propylpiperidin-4-yl)oxy]phenyl group, 3,5-difluoro-4-[(N-n-propylpiperidin-4-yl)oxy]phenyl group, 4-[(N-n-butylpiperidin-4-yl)oxy]phenyl group, 4-[(N-n-butylpiperidin-4-yl)oxy]-3-fluorophenyl group, 4-[(N-n-butylpiperidin-4-yl)oxy]-3,5-difluorophenyl group, 4-[(N-hydroxyacetylpiperidin-4-yl)oxy]phenyl group, 3-fluoro-4-[(N-hydroxyacetylpiperidin-4-yl)oxy]phenyl group, 3,5-difluoro-4-[(N-hydroxyacetylpiperidin-4-yl)oxy]phenyl group, 4-[[N-(3-methoxypropionyl)piperidin-4-yl]oxy]phenyl group, 3-fluoro-4-[[N-(3-methoxypropionyl)piperidine-4-yl]oxy]phenyl group, 3,5-difluoro-4-[[N-(3-methoxypropionyl)piperidine-4-yl]oxy]phenyl group, indan-5-yl group, 1,2,3,4-tetrahydronaphthalen-6-yl group and 1-indanon-5-yl group, but examples are not restricted to these compounds.

The thiourea derivatives of the present invention that are represented by general formula (I) have one asymmetrical carbon atom on the oxazolidine ring, and there are cases where one or more additional asymmetric carbon atoms are present, depending on the types of substituents. The asymmetric carbon atoms that are present in the compound of the present invention can each assume the (S) or (R) configuration, and there are cases

where isomers such as optical isomers and diastereomers are present based on the one or more asymmetrical carbon atoms. Pure isomeric compounds, any mixture of isomers and racemic mixtures are all within the scope of the present invention.

The thiourea derivatives of the present invention represented by general formula (I) can be converted into salts as desired, and preferably pharmacologically permissible salts. Examples of salts of compounds of the present invention are preferably pharmacologically permissible salts, and examples of acid addition salts that may be cited include hydrochlorides, hydrobromides, nitrates, sulfates, hydroiodides, phosphates and other inorganic salts, and acetates, maleates, fumarates, citrates, oxalates, malates, methanesulfonates, p-toluenesulfonates, mandelates, 10-camphorsulfonates, tartrates, lactates, 5-oxotetrahydrofuran-2-carboxylates, 2-hydroxyglutarates and other organic salts. In addition, examples of alkali addition salts that may be used include sodium salts, potassium salts, calcium salts, magnesium salts, ammonium salts and other inorganic alkali salts, and ethanolamine salts, N,N-dialkylethanolamine salts, triethanolamine salts, piperidine salts, piperazine salts, morpholino salts, thiomorpholino salts and other organic salts.

The thiourea derivative or salt thereof of the present invention expressed by general formula (I) can be present in any desired crystal form depending on the manufacture conditions, and although the derivatives may be present as hydrates or solvated compounds, these various crystal forms, hydrates, solvated compounds and mixtures thereof are also within the scope of the present invention.

The following compounds can be offered as preferred compound represented by general formula (I), but the scope of the present invention is not restricted to these examples.

(1) N-(2-Oxo-2-phenyloxazolidin-5-yl)methylthiourea

(2) (S)-N-(2-Oxo-3-phenyloxazolidin-5-yl)methylthiourea;

(3) N-Methyl-N'-(2-oxo-3-phenyloxazolidin-5-yl)methylthiourea;

(4) (S)-N-Methyl-N'-(2-oxo-3-phenyloxazolidin-5-yl)methylthiourea;

(5) (S)-N-[3-(4-Methylphenyl)-2-oxooxazolidin-5-yl]methylthiourea;

(6) (S)-N-Methyl-N'-[3-(4-methylphenyl)-2-oxooxazolidin-5-yl]methylthiourea;

(7) N-[3-(4-Methylphenyl)-2-oxooxazolidin-5-yl]methylthiourea

(8) N-Methyl-N'-[3-(4-methylphenyl)-2-oxooxazolidin-5-yl]methylthiourea;

(9) (S)-N-[3-(3-Methylphenyl)-2-oxooxazolidin-5-yl]methylthiourea;

(10) (S)-N-Methyl-N'-[3-(3-methylphenyl)-2-oxooxazolidin-5-yl]methylthiourea;

(11) (S)-N-[3-(3,4-dimethylphenyl)-2-oxooxazolidin-5-yl]methylthiourea;

(12) (S)-N-[3-(3,4-Dimethylphenyl)-2-oxazolidin-5-yl]methyl-N'-methylthiourea;

(13) (S)-N-[3-(4-Ethylphenyl)-2-oxooxazolidin-5-yl]methylthiourea;

(14) (S)-N-[3-(4-Ethylphenyl)-2-oxooxazolidin-5-yl]methyl-N'-methylthiourea;

(15) (S)-N-[2-Oxo-3-(4-n-propylphenyl)oxazolidin-5-yl]methylthiourea;

(16) (S)-N-Methyl-N'-[2-oxo-3-(4-n-propylphenyl)oxazolidin-5-yl]methylthiourea;

(17) (S)-N-[3-(4-Isopropylphenyl)-2-oxooxazolidin-5-yl]methylthiourea;

(18) (S)-N-[3-(4-Isopropylphenyl)-2-oxooxazolidin-5-yl]methyl-N'-methylthiourea;

(19) (S)-N-[3-(4-n-Butylphenyl)-2-oxooxazolidin-5-yl]methylthiourea;

(20) (S)-N-[3-(4-n-Butylphenyl)-2-oxooxazolidin-5-yl]methyl-N'-methylthiourea;

(21) (S)-N-[3-(4-Isobutylphenyl)-2-oxooxazolidin-5-yl]methylthiourea;

(22) (S)-N-[3-(4-Isobutylphenyl)-2-oxooxazolidin-5-yl]methyl-N'-methylthiourea;

(23) (S)-N-[2-Oxo-3-(4-n-pentylphenyl)oxazolidin-5-yl]methylthiourea;

(24) (S)-N-Methyl-N'-[2-oxo-3-(4-n-pentylphenyl)oxazolidin-5-yl]methylthiourea;

(25) (S)-N-[3-(4-n-Hexylphenyl)-2-oxooxazolidin-5-yl]methylthiourea;

(26) (S)-N-[3-(4-n-Hexylphenyl)-2-oxooxazolidin-5-yl]methyl-N'-methylthiourea;

(27) (S)-N-[3-(4-Methoxyphenyl)-2-oxooxazolidin-5-yl]methylthiourea;

(28) (S)-N-[3-(4-Methoxyphenyl)-2-oxooxazolidin-5-yl]methyl-N'-methylthiourea;

(29) (S)-N-[3-(4-Ethoxyphenyl)-2-oxooxazolidin-5-yl]methylthiourea;

(30) (S)-N-[3-(4-Ethoxyphenyl)-2-oxooxazolidin-5-yl]methyl-N'-methylthiourea;

(31) (S)-N-[2-Oxo-3-(4-n-propoxyphenyl)oxazolidin-5-yl]methylthiourea;

(32) (S)-N-Methyl-N'-[2-oxo-3-(4-n-propoxyphenyl)oxazolidin-5-yl]methylthiourea;

(33) (S)-N-[3-(4-Isopropoxyphenyl)-2-oxooxazolidin-5-yl]methylthiourea;

(34) (S)-N-[3-(4-Isopropoxyphenyl)-2-oxooxazolidin-5-yl]methyl-N'-methylthiourea;

(35) (S)-N-[3-(4-n-Butoxyphenyl)-2-oxooxazolidin-5-yl]methylthiourea;

(36) (S)-N-[3-(4-n-Butoxyphenyl)-2-oxooxazolidin-5-yl]methyl-N'-methylthiourea;

(37) (S)-N-[2-Oxo-3-(4-n-pentyloxyphenyl)oxazolidin-5-yl]methylthiourea;

(38) (S)-N-Methyl-N'-[2-oxo-3-(4-n-pentyloxyphenyl)-oxazolidin-5-yl]methylthiourea;

(39) (S)-N-[3-(4-n-Hexyloxyphenyl)-2-oxooxazolidin-5-yl]methylthiourea;
(40) (S)-N-[3-(4-n-Hexyloxyphenyl)-2-oxooxazolidin-5-yl]methyl-N'-methylthiourea;
(41) (S)-N-[3-(4-Acetylphenyl)-2-oxooxazolidin-5-yl]methylthiourea;
(42) (S)-N-[3-(4-Acetylphenyl)-2-oxooxazolidin-5-yl]methyl-N'-methylthiourea;
(43) (S)-N-[2-Oxo-3-(4-propionylphenyl)oxazolidin-5-yl]methylthiourea;
(44) (S)-N-Methyl-N'-[2-oxo-3-(4-propionylphenyl)oxazolidin-5-yl]methylthiourea;
(45) (S)-N-[3-(4-Butyrylphenyl)-2-oxooxazolidin-5-yl]methylthiourea;
(46) (S)-N-[3-(4-Butyrylphenyl)-2-oxooxazolidin-5-yl]methyl-N'-methylthiourea;
(47) (S)-N-[3-(4-Isobutyrylphenyl)-2-oxooxazolidin-5-yl]methylthiourea;
(48) (S)-N-[3-(4-Isobutyrylphenyl)-2-oxooxazolidin-5-yl]methyl-N'-methylthiourea;
(49) (S)-N-[2-Oxo-3-(4-valerylphenyl)oxazolidin-5-yl]methylthiourea;
(50) (S)-N-Methyl-N'-[2-oxo-3-(4-valerylphenyl)oxazolidin-5-yl]methylthiourea;
(51) (S)-N-[3-[4-(2-Dimethylaminoethoxy)-3-fluorophenyl]-2-oxooxazolidin-5-yl]methylthiourea;
(52) (S)-N-[3-[4-(3-Dimethylaminopropoxy)-3-fluorophenyl]-2-oxooxazolidin-5-yl]methylthiourea;
(53) (S)-N-[3-[4-(4-Dimethylaminobutoxy)-3-fluorophenyl]-2-oxooxazolidin-5-yl]methylthiourea;
(54) (S)-N-[3-[3-Fluoro-4-(2-methoxyethoxy)phenyl]-2-oxooxazolidin-5-yl]methylthiourea;
(55) (S)-N-[3-[3-Fluoro-4-(2-methoxyethoxy)phenyl]-2-oxooxazolidin-5-yl]methyl-N'-methylthiourea;
(56) (S)-N-[3-[4-(Azetidin-1-yl)phenyl]-2-oxooxazolidin-5-yl]methylthiourea;
(57) (S)-N-[3-[4-(Azetidin-1-yl)phenyl]-2-oxooxazolidin-5-yl]methyl-N'-methylthiourea;
(58) (S)-N-[3-[4-(Azetidin-1-yl)-3-fluorophenyl]-2-oxooxazolidin-5-yl]methylthiourea;
(59) (S)-N-[3-[4-(Azetidin-1-yl)-3-fluorophenyl]-2-oxooxazolidin-5-yl]methylthiourea;
(59) (S)-N-[3-[4-(Azetidin-1-yl)-3-fluorophenyl]-2-oxooxazolidin-5-yl]methyl-N'-methylthiourea;
(60) (S)-N-[3-[3-Fluoro-4-(3-methoxyazetidin-1-yl)phenyl]-2-oxooxazolidin-5-yl]methylthiourea;

(61) (S)-N-[3-[3-Fluoro-4-(3-methoxyazetidin-1-yl)phenyl]-2-oxooxazolidin-5-yl]methyl-N'-methylthiourea;
(62) (S)-N-[3-[3-Fluoro-4-[3-(2-methoxyethoxy)azetidin-1-yl]phenyl]-2-oxooxazolidin-5-yl]methylthiourea;
(63) (S)-N-[3-[3-Fluoro-4-[3-(2-methoxyethoxy)azetidin-1-yl]phenyl]-2-oxooxazolidin-5-yl]methyl-N'-methylthiourea;
(64) (S)-N-[2-Oxo-3-[4-(pyrrolidin-1-yl)phenyl]oxazolidin-5-yl]methylthiourea;
(65) (S)-N-Methyl-N'-[2-oxo-3-[4-(pyrrolidin-1-yl)phenyl]oxazolidin-5-yl]methylthiourea;
(66) (S)-N-[3-[3-Fluoro-4-(pyrrolidin-1-yl)phenyl]-2-oxooxazolidin-5-yl]methylthiourea;
(67) (S)-N-[3-[3-Fluoro-4-(pyrrolidin-1-yl)phenyl]-2-oxooxazolidin-5-yl]methyl-N'-methylthiourea;
(68) (S)-N-[2-Oxo-3-[4-(piperidine-1-yl)phenyl]oxazolidin-5-yl]methylthiourea;
(69) (S)-N-Methyl-N'-[2-oxo-3-[4-(piperidine-1-yl)phenyl]oxazolidin-5-yl]methylthiourea;
(70) (S)-N-[3-[3-Fluoro-4-(piperidine-1-yl)phenyl]-2-oxooxazolidin-5-yl]methylthiourea;
(71) (S)-N-[3-[3-Fluoro-4-(piperidine-1-yl)phenyl]-2-oxooxazolidin-5-yl]methyl-N'-methylthiourea;
(72) (S)-N-[3-[3-Fluoro-4-(4-methoxypiperidin-1-yl)phenyl]-2-oxooxazolidin-5-yl]methylthiourea;
(73) (S)-N-[3-[3-Fluoro-4-(4-methoxypiperidin-1-yl)phenyl]-2-oxooxazolidin-5-yl]methyl-N'-methylthiourea
(74) (S)-N-[3-[3-Fluoro-4-[4-(2-methoxyethoxy)piperidine-1-yl]phenyl]-2-oxooxazolidin-5-yl]methylthiourea;
(75) (S)-N-[3-[3-Fluoro-4-[4-(2-methoxyethoxy)piperidine-1-yl]phenyl]-2-oxooxazolidin-5-yl]methyl-N'-methylthiourea;
(76) (S)-N-[3-[4-(Morpholin-4-yl)phenyl]-2-oxooxazolidin-5-yl]methylthiourea;
(77) (S)-N-Methyl-N'-[3-[4-(morpholin-4-yl)phenyl]-2-oxooxazolidin-5-yl]methylthiourea;
(78) N-[3-[3-Fluoro-4-(morpholin-4-yl)phenyl]-2-oxooxazolidin-5-yl]methylthiourea;

(79) N-[3-[3-Fluoro-4-(morpholin-4-yl)phenyl]-2-oxooxazolidin-5-yl]methyl-N'-methylthiourea;
(80) (S)-N-[3-[3-Fluoro-4-(morpholin-4-yl)phenyl]-2-oxooxazolidin-5-yl]methylthiourea;
(81) (S)-N-[3-[3-Fluoro-4-(morpholin-4-yl)phenyl]-2-oxooxazolidin-5-yl]methyl-N'-methylthiourea;
(82) (S)-N-[2-Oxo-3-[4-(thiomorpholin-4-yl)phenyl]oxazolidin-5-yl]methylthiourea;
(83) (S)-N-Methyl-N'-[2-oxo-3-[4-(thiomorpholin-4-yl)phenyl]oxazolidin-5-yl]methylthiourea;
(84) N-[3-[3-Fluoro-4-(thiomorpholin-4-yl)phenyl]-2-oxooxazolidin-5-yl]methylthiourea;
(85) N-[3-[3-Fluoro-4-(thiomorpholin-4-yl)phenyl]-2-oxooxazolidin-5-yl]methyl-N'-methylthiourea;
(86) (S)-N-[3-[3-Fluoro-4-(thiomorpholin-4-yl)phenyl]-2-oxooxazolidin-5-yl]methylthiourea;
(87) (S)-N-[3-[3-Fluoro-4-(thiomorpholin-4-yl)phenyl]-2-oxooxazolidin-5-yl]methyl-N'-methylthiourea;
(88) (S)-N-[3-[4-(1-Oxidothiomorpholin-4-yl)phenyl]-2-oxooxazolidin-5-yl]methylthiourea;
(89) (S)-N-Methyl-N'-[3-[4-(1-oxidothiomorpholin-4-yl)phenyl]-2-oxooxazolidin-5-yl]methylthiourea;
(90) (S)-N-[3-[3-Fluoro-4-(1-oxidothiomorpholin-4-yl)phenyl]-2-oxooxazolidin-5-yl]methylthiourea;
(91) (S)-N-[3-[3-Fluoro-4-(1-oxidothiomorpholin-4-yl)phenyl]-2-oxooxazolidin-5-yl]methyl-N'-methylthiourea;
(92) (S)-N-[3-[4-(1,1-Dioxidothiomorpholin-4-yl)phenyl]-2-oxooxazolidin-5-yl]methylthiourea;
(93) (S)-N-[3-[4-(1,1-Dioxidothiomorpholin-4-yl)phenyl]-2-oxooxazolidin-5-yl]methyl-N'-methylthiourea;
(94) (S)-N-[3-[4-(1,1-Dioxidothiomorpholin-4-yl)-3-fluorophenyl]-2-oxooxazolidin-5-yl]methylthiourea;

(95) (S)-N-[3-[4-(1,1-Dioxidothiomorpholin-4-yl)-3-fluorophenyl]-2-oxooxazolidin-5-yl]methyl-N'-methylthiourea;

(96) (S)-N-[2-Oxo-3-[4-(piperazin-1-yl)phenyl]oxazolidin-5-yl]methylthiourea;

(97) (S)-N-Methyl-N'-[2-oxo-3-[4-(piperazin-1-yl)phenyl]oxazolidin-5-yl]methylthiourea;

(98) (S)-N-[3-[3-Fluoro-4-(piperazin-1-yl)phenyl]-2-oxooxazolidin-5-yl]methylthiourea;

(99) (S)-N-[3-[3-Fluoro-4-(piperazin-1-yl)phenyl]-2-oxooxazolidin-5-yl]methyl-N-methylthiourea;

(100) (S)-N-[3-[4-(4-Methylpiperazin-1-yl)phenyl]-2-oxooxazolidin-5-yl]methylthiourea;

(101) (S)-N-Methyl-N'-[3-[4-(4-methylpiperazin-1-yl)phenyl]-2-oxooxazolidin-5-yl]methylthiourea;

(102) (S)-N-[3-[3-Fluoro-4-(4-methylpiperazin-1-yl)phenyl]-2-oxooxazolidin-5-yl]methylthiourea;

(103) (S)-N-[3-[3-Fluoro-4-(4-methylpiperazin-1-yl)phenyl]-2-oxooxazolidin-5-yl]methyl-N'-methylthiourea;

(104) (S)-N-[3-[4-(4-n-Butylpiperazin-1-yl)-3-fluorophenyl]-2-oxooxazolidin-5-yl]methylthiourea;

(105) (S)-N-[3-[4-(4-n-Butylpiperazin-1-yl)-3-fluorophenyl]-2-oxooxazolidin-5-yl]methyl-N'-methylthiourea;

(106) (S)-N-[3-[4-(4-Hydroxyacetylpiperazin-1-yl)phenyl]-2-oxooxazolidin-5-yl]methylthiourea;

(107) (S)-N-[3-[4-(4-Hydroxyacetylpiperazin-1-yl)phenyl]-2-oxooxazolidin-5-yl]methyl-N'-methylthiourea;

(108) (S)-N-[3-[3-Fluoro-4-(4-hydroxyacetylpiperazin-1-yl)phenyl]-2-oxooxazolidin-5-yl]methylthiourea;

(109) (S)-N-[3-[3-Fluoro-4-(4-hydroxyacetylpiperazin-1-yl)phenyl]-2-oxooxazolidin-5-yl]methyl-N'-methylthiourea;

(110) (S)-N-Ethyl-N'-(2-oxo-3-phenyloxazolidin-5-yl)methylthiourea;

(111) (S)-N-(2-Oxo-3-phenyloxazolidin-5-yl)methyl-N'-n-propylthiourea;

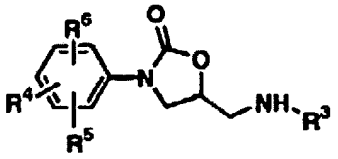
(112) (S)-N-n-Butyl-N'-(2-oxo-3-phenyloxazolidin-5-yl)methylthiourea;

(113) (S)-N-Cyclopropyl-N'-(2-oxo-3-phenyloxazolidin-5-yl)methylthiourea;

(114) (S)-N-Amino-N'-(2-oxo-3-phenyloxazolidin-5-yl)methylthiourea;
(115) (S)-N-Methylamino-N'-(2-oxo-3-phenyloxazolidin-5-yl)methylthiourea;
(116) (S)-N-(2-Oxo-3-phenyloxazolidin-5-yl)methyl-N'-phenylthiourea;
(117) (S)-N-Benzyl-N'-(2-oxo-3-phenyloxazolidin-5-yl)methylthiourea;
(118) (S)-N-[3-(4-Ethenylphenyl)-2-oxooxazolidin-5-yl]methylthiourea;
(119) (S)-N-[3-(4-Methanesulfonylphenyl)-2-oxooxazolidin-5-yl]methylthiourea;
(120) (S)-N-[3-(4-Benzylphenyl)-2-oxooxazolidin-5-yl]methylthiourea;
(121)(S)-N-[3-(4-Methylthiophenyl)-2-oxooxazolidin-5-yl]methylthiourea;
(122) (S)-N-[3-(4-Aminophenyl)-2-oxooxazolidin-5-yl]methylthiourea;
(123) (S)-N-[3-(4-Benzoylphenyl)-2-oxooxazolidin-5-yl]methylthiourea;
(124) (S)-N-[3-[3-Fluoro-4-[4-(3-methoxypropionyl)piperazin-1-yl]phenyl]-2-oxooxazolidin-5-yl]methylthiourea;
(125) (S)-N-[3-[3-Fluoro-4-[4-(3-methoxypropionyl)piperazin-1-yl]phenyl]-2-oxooxazolidin-5-yl]methyl-N'-methylthiourea;
(126) (S)-N-[3-[4-[4-(2-Ethoxycarbonylethyl)piperazin-1-yl]-3-fluorophenyl]-2-oxooxazolidin-5-yl]methylthiourea;
(127) (S)-N-[3-[4-[4-(2-Ethoxycarbonylethyl)piperazin-1-yl]-3-fluorophenyl]-2-oxooxazolidin-5-yl]methyl-N'-methylthiourea;
(128) (S)-N-[2-Oxo-3-(4-phenoxyphenyl)oxazolidin-5-yl]methylthiourea;
(129) (S)-N-[3-[3-Fluoro-4-(pyridin-3-yl)oxyphenyl]-2-oxooxazolidin-5-yl]methylthiourea;
(130) (S)-N-3-(Indan-5-yl)-2-oxooxazolidin-5-yl]methylthiourea;
(131) (S)-N-[3-(Indan-5-yl)-2-oxooxazolidin-5-yl]methyl-N'-methylthiourea;
(132) (S)-N-[2-Oxo-3-(1,2,3,4-tetrahydronaphthalen-6-yl)oxazolidin-5-yl]methylthiourea;
(133) (S)-N-Methyl-N'-[2-oxo-3-(1,2,3,4-tetrahydronaphthalen-6-yl)oxazolidin-5-yl]methylthiourea;
(134) (S)-N-[3-(1-Indanon-5-yl)-2-oxooxazolidin-5-yl]methylthiourea;
(135) (S)-N-[3-(1-Indanon-5-yl)-2-oxooxazolidin-5-yl]methyl-N'-methylthiourea; and
(136) (S)-N-[3-[4-(3-Azabicyclo[3.3.0]octan-3-yl)phenyl]-2-oxooxazolidin-5-yl]methylthiourea.

The thiourea derivatives of the present invention expressed by general formula (I) can be manufactured by the method described below, but the manufacture methods for these compounds are not restricted to these methods. In addition, the compounds represented by general formula (II) above are described in detail in the following manufacture method, but the compounds of the present invention are not restricted to the compounds of general formula (II). In the working examples in this specification, specific and detailed manufacture methods are described for typical thiourea derivative compounds of the present invention. Consequently, a person skilled in the art could readily produce any of the compounds of the present invention encompassed by general formula (I) above by means of appropriate modifications or alterations to these methods carried out as necessary by the appropriate selection of raw material compounds, reaction reagents and reaction conditions in reference to the following general discussion and specific descriptions of the working examples.

In the first mode of the manufacture method for thiourea derivatives of the present invention, compounds wherein R^2 in the compound represented by general formula (II) above is a hydrogen atom can be manufactured by allowing a 5-aminomethyl-3-aryl-2-oxooxazolidine derivative represented by general formula (III) below:



(III)

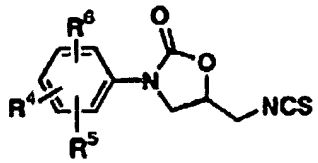
(in the formula, R^3, R^4, R^5 and R^6 have the same meanings as above)
and a isothiocyanate derivative represented by general formula (IV) below:
SCN-R^1 (in the formula, R^1 has the same meaning as above) to react in the presence or absence of solvent and in the presence or absence of base, followed by deprotection carried out as necessary.

Any solvent may be used as the solvent used in the reaction between the compound represented by general formula (III) and the compound represented by general formula (IV), provided that it does not hinder the reaction, and examples that may be cited include methanol, ethanol, n-butanol, sec-butanol, tert-butanol and other alcohol solvents, acetone, acetonitrile, N,N-dimethylformamide, N-methyl-2-pyrrolidone, dimethylsulfoxide, tetramethylene sulfone, tetramethylene sulfoxide,

hexamethylphosphoric triamide and other aprotic polar solvents, diethyl ether, diisopropyl ether, tetrahydrofuran and other ether-based solvents, methyl acetate, ethyl acetate and other ester-based solvents, benzene, toluene and other aromatic hydrocarbon-based solvents, pyridine, picoline, lutidine, collidine and other organic base solvents, dichloromethane, 1,2-dichloroethane, chloroform and other halogenated hydrocarbon-based solvents and mixed solvents formed therefrom. In addition, examples of bases that may be cited include triethylamine, diisopropylethylamine, 4-dimethylaminopyridine, 1,8-diazabicyclo[5.4.0]-7-undecene, 1,2,2,6,6-pentamethylpiperidine and other organic bases or sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogen carbonate, potassium hydrogen carbonate and other inorganic bases. All of the reactions are carried out at temperatures ranging from chilling on ice to 200°C.

The deprotection reaction in the manufacture method can be carried out by various methods depending on the type of nitrogen atom protective groups R^1 and R^3. For example, when R^1 and R^3 are protective groups that form amido structures such as lower alkanoyl groups, halogeno-lower alkanoyl groups and arylcarbonyl groups, manufacture involves deprotection by means of a hydrolysis reaction employing acid or alkali. Amide hydrolysis reactions can be carried out using acids such as hydrochloric acid or sulfuric acid for acid hydrolysis, and alkali hydrolysis can be carried out using alkali agents such as sodium hydroxide and potassium hydroxide in accordance with methods that are themselves well known. These acids or alkalis can be used in the form of aqueous solutions, but may also be used as organic solvents such as methanol, ethanol, n-butanol, sec-butanol and tert-butanol or as hydrous organic solvents. In addition, the reaction can be carried out at temperatures ranging from room temperature to the reflux temperature of the solvent. In addition, when the nitrogen atom protective groups R^1 and R^3 are aryloxycarbonyl groups, aralkyloxycarbonyl groups, lower alkyloxycarbonyl groups or other protective groups having urethane structures, the derivatives can be manufactured by performing deprotection by treatment with hydrochloric acid, hydrobromic acid, trifluoroacetic acid and other acid in the absence of solvent or in a solvent such as acetic acid, ethyl acetate, 1,4-dioxane, water, methanol, ethanol and mixtures thereof. The reaction can be carried out at temperatures ranging from chilling on ice to 200°C.

In a second mode of the manufacture method for the compounds of the present invention, compounds wherein R^3 in the compounds represented by general formula (II) above are hydrogen atoms can be manufactured by means of allowing a reaction to occur between an isothiocyanate derivative represented by general formula (V) below:



(V)

(in the formula, R^4, R^5 and R^6 have the same meanings as above)
and an amine derivative represented by general formula (VI) below:
R^1-NH-R^2 (in the formula, R^1 and R^2 have the same meanings as above) in the presence or absence of solvent, where a deprotection reaction is also carried out as necessary.

Any solvent may be used as the solvent used in the reaction between the compound represented by general formula (V) and the compound represented by general formula (VI), provided that it does not hinder the reaction, and examples that may be cited include methanol, ethanol, n-butanol, sec-butanol, tert-butanol and other alcohol solvents, acetone, acetonitrile, N,N-dimethylformamide, N-methyl-2-pyrrolidone, dimethylsulfoxide, tetramethylene sulfone, tetramethylene sulfoxide, hexamethylphosphoric triamide and other aprotic polar solvents, diethyl ether, diisopropyl ether, tetrahydrofuran and other ether-based solvents, methyl acetate, ethyl acetate and other ester-based solvents, benzene, toluene and other aromatic hydrocarbon-based solvents, pyridine, picoline, lutidine, collidine and other organic base solvents, dichloromethane, 1,2-dichloroethane, chloroform and other halogenated hydrocarbon-based solvents and mixed solvents formed therefrom. The reaction is carried out at temperatures ranging from chilling on ice to 200°C.

The deprotection reaction in this manufacture method can be readily carried out by treatment with acid or a hydrolysis reaction carried out under the deprotection reaction conditions described with respect to the first manufacture mode in accordance with the type of the nitrogen atom protective groups R^1 and R^2.

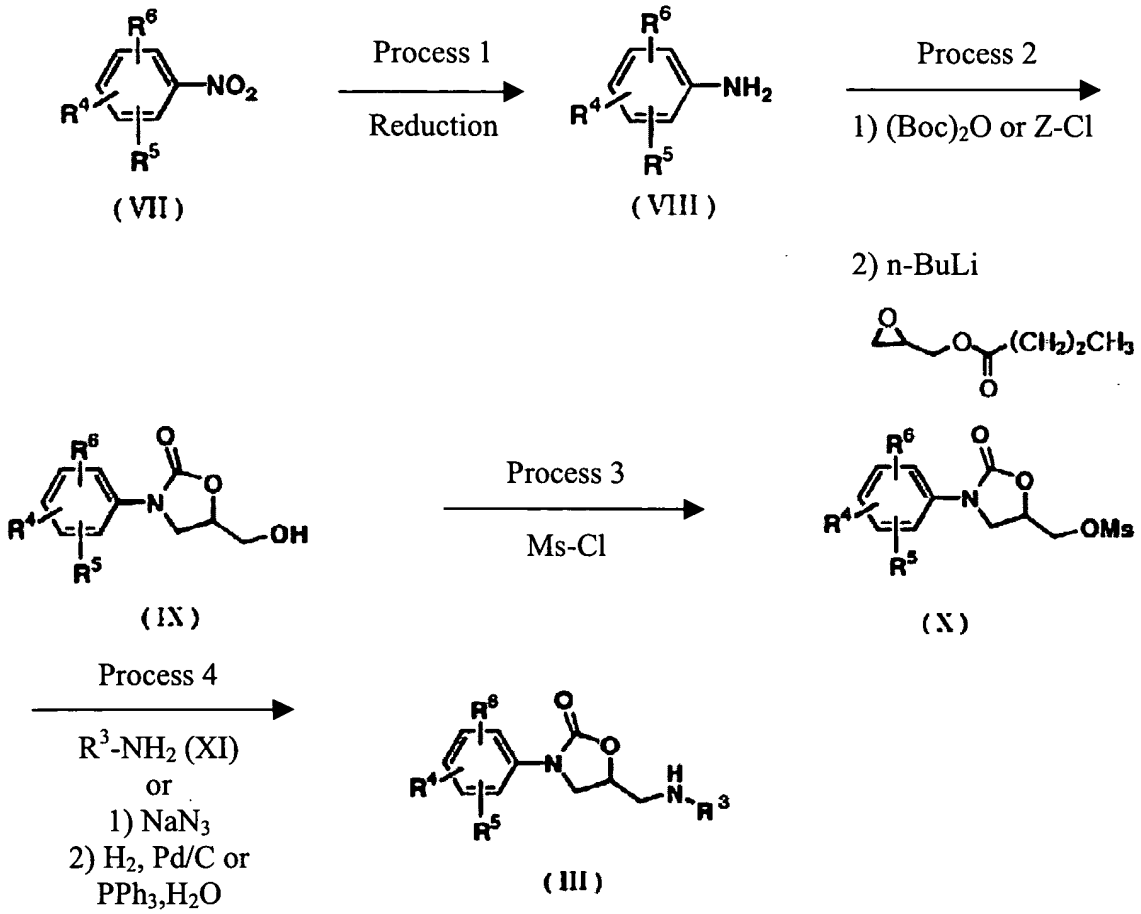
The following methods can be cited as methods for manufacturing the thiourea derivatives of the present invention. Specifically, among the compounds represented by general formula (II) above, when the substituents represented by R^4-R^6 or the groups

that can be substituted on the groups represented by R^4-R^6 are protective groups, the compounds of the present invention can be manufactured by carrying out the deprotection reaction in accordance with the first or second manufacture mode described above. In addition, of the compounds represented by general formula (II) above, it is possible to manufacture the compounds of the present invention by converting the substituents represented by R^4-R^6 or the groups substituted on the groups represented by R^4-R^6 to stable desirable substituents by means of oxidation or reduction using common methods.

Examples of oxidation reactions in the manufacture method that may be cited are oxidation reactions using dimethylsulfoxide and oxallyl chloride at a temperature from -78°C to the reflux temperature of the solvent which are carried out in the presence of a base such as triethylamine, potassium carbonate, sodium carbonate or sodium hydrogen carbonate and in a solvent such as tetrahydrofuran, toluene, N,N-dimethylformamide, dichloromethane, 1,2-dichloroethane or chloroform, or acidification reactions carried out using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone or other quinine in a solvent such as benzene, 1,4-dioxane or toluene at a temperature ranging from chilling on ice to the reflux temperature of the solvent. In addition, other oxidation reactions that may be cited are oxidation reactions carried out by a reaction using chrome oxide, pyridinium chlorochromate or other chromic acid in solvent and in the presence of acid or base. Examples of acids used in the reaction that may be cited include hydrochloric acid, sulfuric acid and acetic acid, and examples of bases that may be cited include pyridine and collidine. Any solvent that does not impede the reaction may be used as the solvent used for the reaction, and examples that may be cited include acetone, acetonitrile, N,N-dimethylformamide, N-methyl-2-pyrrolidone, dimethyl sulfoxide, tetramethylene sulfone, tetramethylene sulfoxide, hexamethyl phosphoric triamide and other aprotic polar solvents, diethyl ether, diisopropyl ether, tetrahydrofuran and other ether-based solvents, methyl acetate, ethyl acetate and other ester-based solvents, benzene, toluene and other aromatic hydrocarbon-based solvents, pyridine, picoline, lutidine, collidine and other organic base solvents, dichloromethane, 1,2-dichloroethane, chloroform and other halogenated hydrocarbon-based solvents and mixed solvents formed therefrom. The reaction is carried out at temperatures ranging from chilling on ice to the reflux temperature of the solvent.

Examples of the reduction reaction that may be cited are reduction reactions carried out using reducing agents such as lithium borohydride and sodium borohydride. Examples of solvents that may be used are methanol, ethanol, n-butanol, sec-butanol, tert-butanol and other alcohol-based solvents, and diethyl ether, diisopropyl ether, tetrahydrofuran and other ether-based solvents. The reaction is carried out at temperatures ranging from chilling on ice to the reflux temperature of the solvent.

In the manufacture method for the compounds of the present invention, some of the 5-aminomethyl-3-allyl-2-oxooxazolidine derivatives represented by general formula (III) used as raw materials are known compounds for which manufacture methods and other information has been previously disclosed in Japanese Unexamined Patent Application No. Hei 8-73455 and the *Journal of Medicinal Chemistry* 39, 673, 680 (1996). In addition, the novel compounds can be manufactured by the methods described below, and details concerning the manufacture methods are described in the reference examples.



(VII) (VIII) (IX) (X) (III)

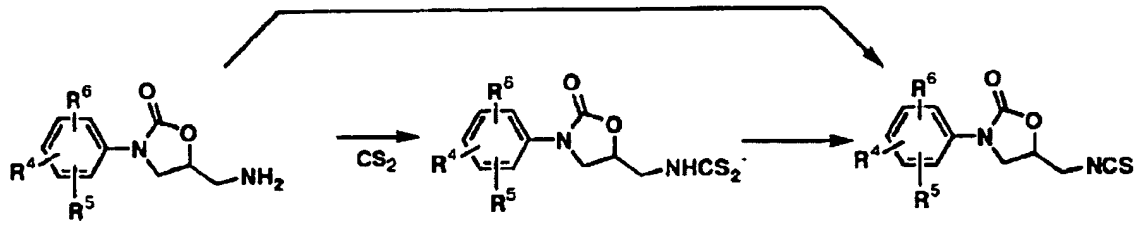
(in the formula, Boc denotes a tert-butoxycarbonyl group, Z denotes a benzyloxycarbonyl group, Ms denotes a methanesulfonyl group, Ph denotes a phenyl group, and R^3, R^4, R^5 and R^6 have the same meanings as above).

In process 1, the compound represented by general formula (VII) is subjected to nitro group reduction using an appropriate method such as a hydrogenation reduction method using a catalyst such as platinum oxide, Raney nickel or palladium-carbon, or a reduction method involving the use of iron powder and hydrochloric acid, acetic acid or the like, thus producing the compound represented by general formula (VIII). In process 2, the compound represented by general formula (VIII) is subjected to urethanation with di-tert-butyl dicarbonate using an appropriate solvent such as methanol or tetrahydrofuran. Alternatively, the compound is subjected to urethanation using benzyloxycarbonyl chloride in the presence of a base such as triethylamine, potassium

carbonate, sodium carbonate or sodium bicarbonate. A reaction is then carried out at a temperature ranging from -78°C to the reflux temperature of the solvent in the presence of glycidyl butyrate and base such as n-butyl lithium and in a solvent such as tetrahydrofuran and N,N-dimethylformamide. The compound represented by general formula (IX) is thus produced.

In process 3, the compound represented by general formula (IX) is subjected to a reaction carried out at a temperature ranging from chilling on ice to the reflux temperature of the solvent using methanesulfonyl chloride in the presence of base such as triethylamine and in a solvent such as tetrahydrofuran, thus producing the compound represented by general formula (X). In process 4, a reaction is allowed to occur between the compound represented by general formula (X) and compound represented by general formula (XI) in a solvent such as methanol at a temperature ranging from chilling on ice to the reflux temperature of the solvent, thus producing the compound represented by general formula (III). Alternatively, the compound represented by general formula (X) is subjected to azidation using sodium azide in a solvent such as tetrahydrofuran or N,N-dimethylformamide. An appropriate reduction method is then carried out such as hydrogenation using a catalyst such as platinum oxide or palladium-carbon or azido group reduction using triphenylphosphine and water to obtain a compound represented by general formula (III) wherein R^3 is a hydrogen atom.

In addition, the isothiocyanate derivatives represented by general formula (V) used as raw material in the manufacture method of the compounds of the present invention are also novel compounds, and can be manufactured in the manner described below:



(V)

(in the formula, R^4, R^5 and R^6 have the same meanings as above).

Specifically, after production of dithiocarbamate by a reaction between carbon disulfide and 5-aminomethyl-3-aryl-2-oxooxazolidine derivative in the presence of base such as triethylamine and in a solvent such as tetrahydrofuran, the compound represented

by general formula (V) is produced by allowing a reaction to occur with ethyl chlorocarbonate, or alternatively, copper sulfate, iron nitrate, iron sulfate, zinc sulfide or other such compound. In addition, other manufacture methods are a manufacture method carried out by allowing thiophosgene to act on 5-aminomethyl-3-aryl-2-oxooxazolidine derivative in the presence of base and the manufacture method presented in organic Synthesis Collective Volume 1, 447 wherein isothiocyanate derivative (V) is derived directly by a common method. Details regarding these manufactures methods are described in the reference examples.

The drugs of the present invention are characterized by containing the thiourea derivatives expressed by general formula (I) or salts thereof as effective components. The effective components of the drugs of the present invention can be substances selected from a group comprising the free form of the aforementioned compounds and pharmacologically permissible salts thereof and salvation products or hydrates thereof, where two or more types thereof may be used in combination. The aforementioned substances themselves may be used as the drugs of the present invention but, in general, the drugs are preferably offered in drug composition configurations that contain one or more preparation additives along with the above substances that are used as effective components.

There are no particular restrictions on the configuration of the drug composition, and the composition may be prepared as a drug composition for oral administration such as a capsule, tablet, fine powder, granule, dispersion or syrup, or as a non-oral drug composition such as an injection agent, suppository, eye drop, eye ointment, ear drop, transdermal agent, trans-mucosal agent, inhalant or topical agent. These preparations can be produced by common methods involving the addition of preparation additives that are pharmacologically and pharmaceutically permissible. In producing oral compositions and suppositories, excipients (e.g., lactose, D-mannitol, corn starch, crystalline cellulose), disintegration agents (e.g., carboxymethylcellulose and carboxymethylcellulose calcium), binders (e.g., hydroxypropylcellulose, hydroxypropylmethylcellulose and polyvinylpyrrolidone), lubricants (e.g., magnesium stearate and talc), coating agents (e.g., hydroxypropylmethylcellulose, white sugar and titanium oxide), plasticizers (e.g., polyethylene glycol), bases (e.g., polyethylene glycol and hard fats) and other

preparation additives may be used. In manufacturing injection agents, eye drops or ear drops, aqueous media, dissolution agents and dissolution aids that allow the production of dissolving dosage forms (e.g., distilled water for injections, physiological saline and propylene glycol), pH adjusters (inorganic or organic acids or bases), isotonic agents (e.g., sodium chloride, fructose and glycerin), stabilizers and other preparation components may be used. For eye ointments and topical agents, appropriate preparation components such as ointments, creams and patches (e.g., white petroleum jelly, macrogols, glycerin, fluidized paraffin and cotton cloth) may be used.

The drugs of the present invention can be administered, for example, as antimicrobial agents for the treatment or prevention of diseases in mammals including humans. The dosage of drug of the present invention has no particular restrictions, and appropriate dosages can be selected in accordance with the type of pathogenic microorganism, the age and weight of the patients and the severity of the disease. Ordinarily, the drug is administered at about 10-2000 mg orally per day for adults, or about 1-1000 mg perorally. The above dosage can be administered once per day or in multiple divisions. It is most desirable to increase or decrease the dosage appropriately depending on the target of prevention or treatment, the site of infection, the type of pathogenic microorganism and the age and symptoms of the patient.

Working examples

The present invention is described below using working examples and reference examples, but the scope of the present invention is not restricted to these examples. The terms in the table have the following meanings. Me: Methyl group; n-Pr: n-propyl group; Z: benzyloxycarbonyl group; n-Bu: n-butyl group, Boc: tert-butoxycarbonyl group, Ms: methanesulfonyl group, Bn: benzyl group, Et: ethyl group.

Reference Example 1: N-tert-Butoxycarbonyl-4-piperidinol

125 mL of di-tert-butyl dicarbonate was added to a 250 mL anhydrous tetrahydrofuran suspension containing 50.0 g of 4-piperidinol while stirring on ice, and the solution was stirred for 30 min at room temperature. The solvent was evaporated off under reduced pressure to obtain 121 g of light yellow liquid.

IR spectrum ν (liq.) cm^{-1}: 1698, 3684

NMR spectrum ($CDCl_3$) δ ppm:

1.46 (9H, s), 1.47-1.50 (2H, m), 1.81-1.87 (2H, m), 3.01-3.10 (2H, m), 3.73-3.87 (3H, m)

Mass spectrum m/z: 201 (M^+)

The compound of reference Example 2 was obtained in the same manner as in Reference Example 1.

Reference Example 2: N-tert-Butoxycarbonyl-3-azetidinol

Properties: Yellow liquid

IR spectrum ν (liq.) cm^{-1}: 1678, 3416

NMR spectrum (DMSO-d_6) δ ppm:

1.37 (9H, s), 3.55-3.60 (2H, m), 3.95-4.00 (2H, m), 4.30-4.40 (2H, m), 5.50 (1H, d, J=6 Hz)

Reference Example 3: N-tert-Butoxycarbonyl-4-methoxypiperidine

190 mL of an anhydrous N,N-dimethylformamide solution containing 49.0 g of N-tert-butoxycarbonyl-4-piperidinol was added to 300 mL of an anhydrous N,N-dimethylformamide suspension containing 8.77 g of 60% sodium hydroxide while stirring at room temperature, whereupon 30.4 mL of methyl iodide was added dropwise and the solution was stirred for 5 h at room temperature. The reaction solution was added to ice water and was extracted with ethyl acetate. The extract was then washed with saturated sodium chloride aqueous solution and after drying on anhydrous sodium sulfate, the solvent was evaporated off under reduced pressure. The residue was then purified by column chromatography (silica gel, ethyl acetate:n-heptane = 1:2 → 2:1) to obtain 44.1 g of colorless liquid.

IR spectrum ν (liq.) cm^{-1}: 1698

NMR spectrum ($CDCl_3$) δ ppm:

1.45-1.55 (2H, m), 1.46 (9H, s), 1.80-1.90 (2H, m), 3.05-3.15 (2H, m), 3.30-3.40 (1H, m), 3.35 (3H, s), 3.70-3.80 (2H, m)

Mass spectrum m/z: 215 (M^+)

Reference Example 4: N-tert-Butoxycarbonyl-3-(2-methoxyethoxy)azetidine

3 mL of an anhydrous N,N-dimethylformamide solution containing 1.0 g of N-tert-butoxycarbonyl-3-azetidinol was added to 5 mL of an anhydrous N,N-dimethylformamide suspension containing 0.25 g of 60% sodium hydroxide while stirring at room temperature. After stirring for 30 minutes at room temperature, 2 mL of an anhydrous N,N-dimethylformamide solution containing 0.98 g of 2-methoxyethylmethanesulfonate was added dropwise, and the solution was stirred for 4 hour at room temperature. The reaction solution was then added to ice water, and was extracted with ethyl acetate. The extract was washed in sequence with water and saturated sodium chloride aqueous solution, and after drying on anhydrous sodium sulfate, the solvent was evaporated off under reduced pressure. The residue was purified by column chromatography (silica gel, ethyl acetate:n-heptane = 1:3) to obtain 0.67 g of colorless liquid.

IR spectrum ν (liq.) cm^{-1}: 1706

NMR spectrum (DMSO-d_6) δ ppm:

1.37 (9H, s), 3.25 (3H, s), 3.41-3.45 (2H, m), 3.46-3.49 (2H, m), 3.64 (2H, dd, J=9, 4 Hz), 3.98 (2H, dd, J=9, 6.5 Hz), 4.21-4.26 (1H, m)

Reference Example 5: 4-Methoxypiperidine hydrochloride

220 mL of an ethyl acetate solution containing 43.9 g of N-tert-butoxycarbonyl-4-methoxypiperidine was added to 220 mL of ethyl acetate containing 9% hydrogen chloride while stirring on ice, and the solution was stirred for 2.5 h while chilling on ice. The precipitated crystals were filtered to obtain 29.1 g of colorless crystals.

IR spectrum ν (liq.) cm^{-1}: 3448

NMR spectrum ($CDCl_3$) δ ppm:

1.95-2.05 (2H, m), 2.10-2.20 (2H, m), 3.15-3.30 (4H, m), 3.33 (3H, s), 3.50-3.60 (1H, m)

Mass spectrum m/z: 115 (M^+)

The compound of Reference Example 6 was obtained in the same manner as in Reference Example 5.

Reference Example 6: 3-(2-Methoxyethoxy)azetidine

Properties: Light yellow liquid

IR spectrum ν (liq.) cm^{-1}: 3436

NMR spectrum (DMSO-d_6) δ ppm:

3.26 (3H, s), 3.43 (2H, t, J=4.5 Hz), 3.54 (2H, t, J=4.5 Hz), 3.75-3.80 (2H, m). 4.05-4.10 (2H, m), 4.35-4.40 (1H, m)

Mass spectrum m/z: 131 (M^+)

Reference Example 7: 3-Fluoro-4-(4-methoxypiperidin-1-yl)nitrobenzene

15.8 g of 4-methoxypiperidine hydrochloride was added to 150 mL of anhydrous acetonitrile containing 15.0 g of 3,4-difluoronitrobenzene and 41 mL of diisopropylethylamine, and the solution was heated at reflux for 5 h. The solvent was evaporated off under reduced pressure, water and 10% sodium hydroxide aqueous solution were added to the residue to render it alkaline, and extraction was performed with ethyl acetate. The extract was washed with saturated sodium chloride aqueous solution, and after drying on anhydrous sodium sulfate, the solvent was evaporated off under reduced pressure to obtain 24.1 g of yellow-brown liquid.

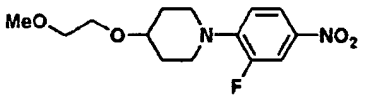
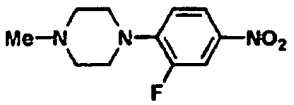
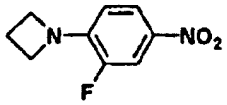
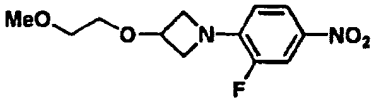
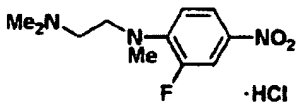
IR spectrum ν (liq.) cm^{-1}: 1336, 1518

NMR spectrum (DMSO-d_6) δ ppm:

1.54-1.62 (2H, m). 1.92-2.00 (2H, m), 3.08-3.16 (2H, m), 3.28 (3H, s), 3.38-3.46 (1H, m), 3.49-3.57 (2H, m), 7.16 (1H, t, J=8.5 Hz), 7.95 (1H, dd, J=14.3 Hz), 7.97 (1H, dd, J=8.5, 3 Hz)

Mass spectrum m/z: 254 (M^+)

The compounds of Reference Examples 8-12 were obtained in the same manner as in Reference Example 7.

Reference example	Chemical formula	Form and physical properties [Recrystallization solvent]
8		Yellow crystals [iso-Pr_2O-n-Heptane] mp, 58.5~59.5°C Elemental analysis $C_{14}H_{19}FN_2O_4$ Theoretical C, 56.37; H, 6.42; N, 9.39 Experimental C, 56.36; H, 6.54; N, 9.34
9		Yellow-brown prisms [iso-Pr_2O] mp, 68~68.5°C Elemental analysis $C_{11}H_{14}FN_3O_2$ Theoretical C, 55.22; H, 5.90; N, 17.56 Experimental C, 55.24; H, 5.71; N, 17.63
10		Yellow needles [iso-PrOH] mp, 94.5~96.5°C Elemental analysis $C_9H_9FN_2O_2$ Theoretical C, 55.10; H, 4.62; N, 14.28 Experimental C, 54.87; H, 4.64; N, 14.27
11		Yellow liquid NMR (DMSO-d_6) δ ppm: 3.27 (3H, s), 3.47 (2H, t, J=4.5Hz), 3.56 (2H, t, J=4.5Hz), 3.95-4.00 (2H, m), 4.35-4.40 (2H, m), 4.45-4.50 (1H, m), 6.57 (1H, t, J=9Hz), 7.89 (1H, dd, J=13, 2.5Hz), 7.93 (1H, dd, J=9, 2.5Hz) IR ν (liq.) cm^{-1}: 1326, 1532 MS(m/z): 270 (M^+)
12		Yellow crystals [EtOH] mp, 193~194°C Elemental analysis $C_{11}H_{16}FN_3O_2 \cdot HCl$ Theoretical C, 47.57; H, 6.17; N,15.13 Experimental C, 47.30; H, 5.89; N, 15.08

Reference Example 13: 4-(2-Dimethylaminoethoxy)-3-fluoronitrobenzene

10 mL of an anhydrous tetrahydrofuran solution containing 3.50 mL of 2-dimethylaminoethanol was added dropwise to 10 mL of an anhydrous tetrahydrofuran suspension containing 1.38 g of 60% sodium hydride while stirring and chilling on ice. After stirring for 30 minutes at the same temperature, 30 mL of an anhydrous tetrahydrofuran solution containing 5.00 g of 3,4-difluoronitrobenzene was added dropwise and the solution was stirred for 30 minutes at room temperature. After adding the reaction solution to ice water, the aqueous layer was extracted with ethyl acetate, and the extract was washed in sequence with water and saturated sodium chloride aqueous solution, before drying on anhydrous sodium sulfate and evaporating off the solvent under reduced pressure. The residue was purified by column chromatography (silica gel, dichloromethane:methanol = 10:1) to obtain 7.60 g of yellow-brown liquid.

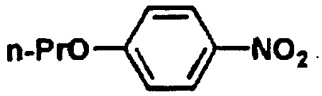
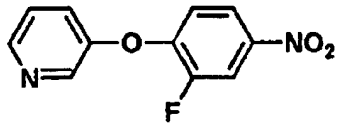
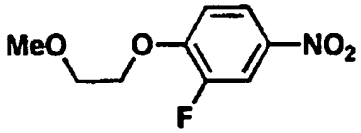
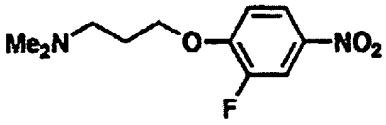
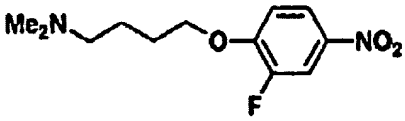
IR spectrum ν (liq.) cm^{-1}: 1348, 1526

NMR spectrum ($CDCl_3$) δ ppm:

2.36 (6H, s), 2.82 (2H, t, J=5.5 Hz), 4.24 (2H, t, J=5.5 Hz), 7.05 (1H, t, J=9 Hz), 8.00 (1H, dd, J=10.5, 2.5 Hz), 8.05 (1H, dd, j=9, 2.5 Hz)

Mass spectrum m/z: 228 (M^+)

The compounds of Reference Examples 14-18 were obtained in the same manner as in Reference Example 13.

Reference example	Chemical formula	Form and physical properties [Recrystallization solvent]
14		Brown liquid NMR(DMSO-d_6) δ ppm: 0.99 (3H, t, J=7.5Hz), 1.77 (2H, sex, J=7.5Hz), 4.09 (2H, t, J=7.5Hz), 7.13 (2H, d, J=9Hz), 8.18 (2H, d, J=9Hz) IR ν (liq.) cm^{-1}: 1342, 1514 MS(m/z): 181 (M^+)
15		Brown liquid NMR($CDCl_3$) δ ppm: 7.07 (1H, dd, J=9, 8Hz), 7.35-7.45 (2H, m), 8.05 (1H, dt, J=10, 2Hz), 8.13 (1H,dd, J=4.5, 1Hz), 8.49 (1H, d, J=3Hz), 8.53 (1H, dd, J=4.5, 1Hz) IR ν (liq.) cm^{-1}: 1348, 1526 MS(m/z): 242 (M^+)
16		Light yellow needles [iso-Pr_2O] mp, 62.5~63°C Elemental analysis $C_9H_{10}FNO_4$ Theoretical C, 50.24; H, 4.68; N, 6.51 Experimental C, 50.18; H, 4.54; N, 6.50
17		Yellow-brown liquid NMR(DMSO-d_6) δ ppm: 1.91 (2H, quin, J=6.5Hz), 2.15 (6H, s), 2.37 (2H, t, J=6.5Hz), 4.25 (2H, t, J=6.5Hz), 7.40 (1H, t, J=9Hz), 8.07-8.13 (2H, m) IR ν (liq.) cm^{-1}: 1348, 1526 MS(m/z): 242 (M^+)
18		Yellow-brown liquid NMR(DMSO-d_6) δ ppm: 1.55 (2H, quin, J=7Hz), 1.79 (2H, quin, J=7Hz), 2.12 (6H, s), 2.25 (2H, t, J=7Hz), 4.23 (2H, t, J=7Hz), 7.40 (1H, t, J=9Hz), 8.06-8.13 (2H, m) IR ν (liq.) cm^{-1}: 1346, 1528 MS(m/z): 256 (M^+)

Reference Example 19: 3-(2-Methoxethoxy)-4-(morpholin-4-yl)nitrobenzene

6.90 mL of 2-methoxyethanol was added dropwise at room temperature to 180 mL of an anhydrous N,N-dimethylformamide suspension containing 4.80 g of 60% sodium hydride, whereupon 18.0 g of 3-fluoro-4-(morpholin-4-yl)nitrobenzene was added, and the solution was stirred for 2 hours at room temperature. The reaction solution was added to ice water and the precipitated crystals were filtered to obtain 19.7 g of yellow-brown crystals. The material was recrystallized from isopropanol to obtain yellow needles with a melting point of 109-110°C.

Elemental analysis $C_{13}H_{18}N_2O_5$

Theoretical: C 55.31; H 6.43; N 9.92

Experimental: C 55.23; H 6.29; N 9.98

The compound of Reference Example 20 was obtained in the same manner as in Reference Example 19.

Reference Example 20: 4-(Morpholin-4-yl)-3-n-propoxynitrobenzene

Form: Yellow prisms (recrystallization solvent: Et_2O)

Melting point: 110-111°C

Elemental analysis $C_{13}H_{18}N_2O_4$

Theoretical: C 58.63; H 6.81; N 10.52

Experimental: C 58.62; H 6.90; N 10.53

Reference Example 21: 4-(2-Dimethylaminoethoxy)-3-fluoroaniline

40 mL of a methanol suspension containing 2.00 g of 4-(2-dimethylaminoethoxy)-3-fluoronitrobenzene and 0.02 g of platinum oxide was stirred for 1.5 hours at normal temperature and at a hydrogen pressure of 2 kg/cm^2. After filtering out the catalyst, the solution was concentrated under reduced pressure to obtain 1.78 g of a yellow-brown liquid.

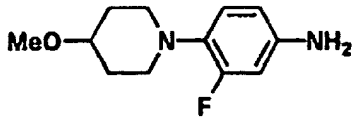
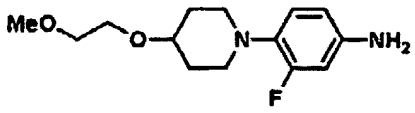
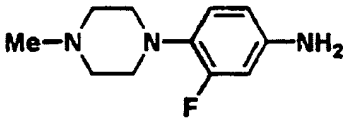
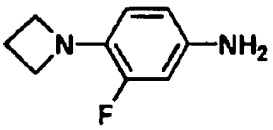
IR spectrum ν (liq.) cm^{-1}: 3352

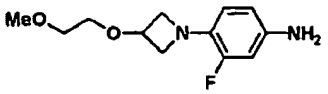
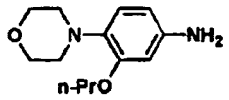
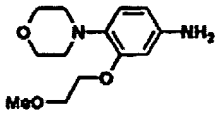
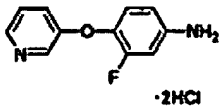
NMR spectrum (DMSO-d_6) δ ppm:

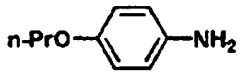
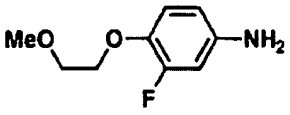
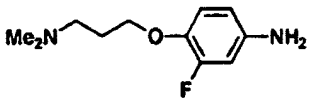
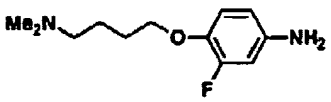
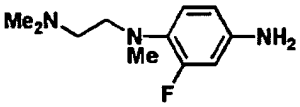
2.20 (6H, s), 2.56 (2H, t, J=6 Hz), 3.93 (2H, t, J=6 Hz), 4.82 (2H, brs), 6.28 (1H, dd, J=9, 2.5 Hz), 6.41 (1H, dd, J=13.5, 2.5 Hz), 6.82 (1H, t, J=9 Hz)

Mass spectrum m/z: 198 (M^+)

The compounds of Reference Examples 22-34 were obtained in the same manner as in Reference Example 21.

Reference example	Chemical formula	Form and physical properties [Recrystallization solvent]
22		Black liquid NMR(DMSO-d_6) δ ppm: 1.49-1.59 (2H, m), 1.86-1.94 (2H, m), 2.59-2.67 (2H, m), 2.97-3.04 (2H, m), 3.22-3.29 (1H, m), 3.25 (3H, s), 4.83 (2H, brs), 6.29 (1H, dd, J=8.5, 2.5Hz), 6.33 (1H, dd, J=14.5, 2.5Hz), 6.75 (1H, t, J=9.5, 8.5Hz) IR ν (liq.) cm^{-1}: 3360, 3448 MS(m/z): 224 (M^+)
23		Brown liquid NMR (DMSO-d_6) δ ppm: 1.50-1.60 (2H, m), 1.85-1.95 (2H, m), 2.60-2.65 (2H, m), 2.95-3.05 (2H, m), 3.26 (3H, s), 3.35-3.40 (1H, m), 3.44 (2H, t, J=5Hz), 3.54 (2H, t, J=5Hz), 4.83 (2H, brs), 6.28 (1H, dd, J=8.5, 2.5Hz), 6.32 (1H, dd, J=14.5, 2.5Hz), 6.75 (1H, t, J=8.5Hz), IR ν (liq.) cm^{-1}: 3364, 3464 MS(m/z): 268 (M^+)
24		Brown prisms [iso-Pr_2O] mp, 87~88°C Elemental analysis $C_{11}H_{16}FN_3$ Theoretical C, 63.13; H, 7.71; N, 20.08 Experimental C, 63.10; H, 7.46; N, 20.08
25		Brown liquid NMR (DMSO-d_6) δ ppm: 2.18 (2H, quin, J=7Hz), 3.68 (4H, t, J=7Hz), 4.58 (2H, brs), 6.15-6.35 (3H, m) IR ν (liq.) cm^{-1}: 3348 MS (m/z): 166 (M^+)

Reference example	Chemical formula	Form and physical properties [Recrystallization solvent]
26		Black liquid NMR (DMSO-d_6) δ ppm: 3.25 (3H, s), 3.40-3.45 (4H, m), 3.50 (2H, t, J=4.5Hz), 3.90-4.00 (2H, m), 4.25-4.35 (1H, m), 4.61 (2H, brs), 6.25-6.35 (3H, m) IR ν (liq.) cm^{-1}: 3360, 3430 MS (m/z): 240 (M^+)
27		Black liquid NMR (DMSO-d_6) δ ppm: 0.99 (3H, t, J=7.5Hz), 1.72 (2H, sex, J=7.5Hz), 2.82 (4H, t, J=5Hz), 3.67 (4H, t, J=5Hz), 3.83 (2H, t, J=7.5Hz), 4.59 (2H, brs), 6.09 (1H, dd, J=8.5, 2.5Hz), 6.23 (1H, d, J=2.5Hz), 6.59 (1H, d, J=8.5Hz) IR ν (liq.) cm^{-1}: 3356, 3448 MS (m/z): 236 (M^+)
28		Light purple crystals [iso-PrOH-n-Hexane] mp, 91.5~92°C Elemental analysis $C_{13}H_{20}N_2O_3$ Theoretical C, 61.88; H, 7.99; N, 11.10 Experimental C, 61.72; H, 7.93; N, 11.05
29		Light brown crystals [EtOH] mp, 193~195°C $C_{11}H_9FN_2O \cdot 2HCl$ Theoretical C, 47.67; H, 4.00; N, 10.11 Experimental C, 47.70; H, 3.83; N, 10.12

Reference example	Chemical formula	Form and physical properties [Recrystallization solvent]
30		Brown liquid NMR (DMSO-d_6) δ ppm: 0.94 (3H, t, J=7.5Hz), 1.65 (2H, sex, J=7.5Hz), 3.77 (2H, t, J=7.5Hz), 4.46 (2H, brs), 6.50 (2H, d, J=9Hz), 6.63 (2H, d, J=9Hz) IR ν (liq.) cm^{-1}: 3368, 3440 MS(m/z): 151 (M^+)
31		Black-brown liquid NMR($CDCl_3$) δ ppm: 3.44 (3H, s), 3.49 (2H, brs), 3.71 (2H, t, J=5Hz), 4.10 (2H, t, J=5Hz), 6.30-6.40 (1H, m), 6.45 (1H, dd, J=12.5, 2.5Hz), 6.84 (1H, t, J=8.5Hz) IR ν (liq.) cm^{-1}: 3368, 3460 MS(m/z): 185 (M^+)
32		Brown liquid NMR(DMSO-d_6) δ ppm: 1.77 (2H, quin, J=7Hz), 2.12 (6H, s), 2.32 (2H, t, J=7Hz), 3.88 (2H, t, J=7Hz), 4.81 (2H, brs), 6.29 (1H, ddd, J=9.5, 2.5, 1.5Hz), 6.38 (1H, dd, J=13.5, 2.5Hz), 6.80 (1H, t, J=9.5Hz) IR ν (liq.) cm^{-1}: 3216, 3360 MS(m/z): 212 (M^+)
33		Red-brown liquid NMR(DMSO-d_6) δ ppm: 1.50 (2H, quin, J=7Hz), 1.65 (2H, quin, J=7Hz), 2.11 (6H, s), 2.22 (2H, t, J=7Hz), 3.87 (2H, t, J=7Hz), 4.80 (2H, brs), 6.29 (1H, dd, J=8.5, 2.5Hz), 6.39 (1H, dd, J=13.5, 2.5Hz), 6.80 (1H, t, J=8.5Hz) IR ν (liq.) cm^{-1}: 3212, 3360
34		Black liquid NMR($CDCl_3$) δ ppm: 2.24 (6H, s), 2.43 (2H, t, J=7.5Hz), 2.75 (3H, s), 3.08 (2H, t, J=7.5Hz), 3.54 (2H, brs), 6.35-6.45 (2H, m), 6.84 (1H, t, J=9Hz) IR ν (liq.) cm^{-1}: 3216, 3336 MS(m/z): 211 (M^+)

Reference Example 35: N-Benzyloxycarbonyl-4-(thiomorpholin-4-yl)aniline

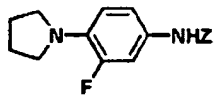
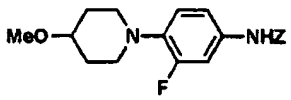
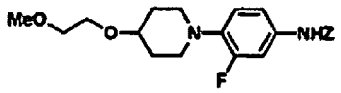
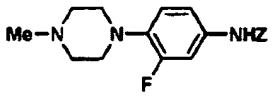
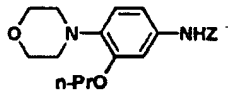
21.0 mL of benzyloxycarbonyl chloride was added dropwise to a mixture of 190 mL of acetone and 190 mL of a 10% sodium carbonate aqueous solution containing 19.0 g of 4-(thiomorpholin-4-yl) while stirring and chilling on ice. After stirring for 30 minutes at room temperature, the precipitated crystals were filtered out and washed with diisopropyl ether to obtain 25.5 g of light brown crystals. The material was recrystallized from a mixture of ethyl acetate-diisopropyl ether to obtain colorless needles with a melting point of 145-146.5°C.

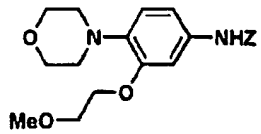
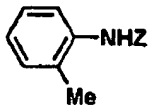
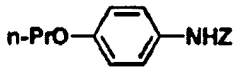
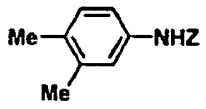
Elemental analysis $C_{18}H_{20}N_2O_2S$

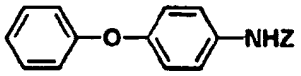
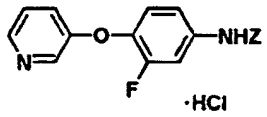
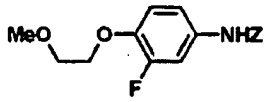
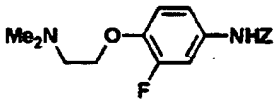
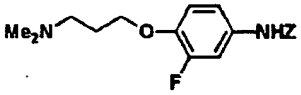
Theoretical C 65.83; H 6.14; N 8.53

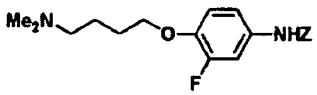
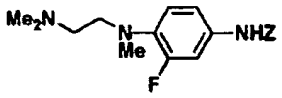
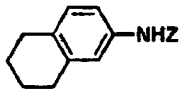
Experimental C 65.69; H 6.12; N 8.38

The compounds of Reference Examples 36-53 were obtained in the same manner as in Reference Example 35.

Reference example	Chemical formula	Form and physical properties [Recrystallization solvent]
36		Light purple needles [iso-PrOH] mp, 120~121°C Elemental analysis $C_{18}H_{19}FN_2O_2$ Theoretical C, 68.77; H, 6.09; N, 8.91 Experimental C, 68.88; H, 6.00; N, 8.88
37		Colorless crystals [AcOEt-iso-Pr2O] mp, 107~108°C Elemental analysis $C_{20}H_{23}FN_2O_3$ Theoretical C, 67.02; H, 6.47; N, 7.82 Experimental C, 66.90; H, 6.35; N, 7.73
38		Light brown crystals [AcOEt-iso-Pr2O] mp, 97~98.5°C Elemental analysis $C_{22}H_{27}FN_2O_4$ Theoretical C, 65.66; H, 6.76; N, 6.96 Experimental C, 65.59; H, 6.98; N, 6.96
39		Colorless needles [iso-PrOH] mp, 136.5~137°C Elemental analysis $C_{19}H_{22}FN_3O_2$ Theoretical C, 66.46; H, 6.46; N, 12.24 Experimental C, 66.50; H, 6.49; N, 12.14
40		Light yellow needles [iso-Pr2O] mp, 110~111°C Elemental analysis $C_{21}H_{26}N_2O_4$ Theoretical C, 68.09; H, 7.07; N, 7.56 Experimental C, 67.91; H, 7.01; N, 7.55

Reference example	Chemical formula	Form and physical properties [Recrystallization solvent]
41		Colorless needles [Et_2O-iso-Pr_2O] mp, 79.5~80.5°C Elemental analysis $C_{21}H_{26}N_2O_5$ Theoretical C, 65.27; H, 6.78; N, 7.25 Experimental C, 65.12; H, 6.67; N, 7.25
42		Colorless needles [iso-Pr_2O] mp, 82~83°C Elemental analysis $C_{15}H_{15}NO_2$ Theoretical C, 74.67; H, 6.27; N, 5.81 Experimental C, 74.57; H, 6.37; N, 5.77
43		Colorless crystals [iso-PrOH] mp, 110~111°C Elemental analysis $C_{17}H_{19}NO_3$ Theoretical C, 71.56; H, 6.71; N, 4.91 Experimental C, 71.52; H, 6.79; N, 4.96
44		Colorless crystals [n-Hexane] mp, 59.5~60.5°C Elemental analysis $C_{18}H_{21}NO_2$ Theoretical C, 76.29; H, 7.47; N, 4.94 Experimental C, 76.31; H, 7.56; N, 4.97
45		Colorless crystals [iso-Pr_2O] mp, 77.5~78°C Elemental analysis $C_{16}H_{17}NO_2$ Theoretical C, 75.27; H, 6.71; N, 5.49 Experimental C, 75.16; H, 6.63; N, 5.51

Reference example	Chemical formula	Form and physical properties [Recrystallization solvent]
46		Colorless needles [AcOEt-n-Hexane] mp, 107~108°C Elemental analysis $C_{20}H_{17}NO_3$ Theoretical C, 75.22; H, 5.37; N, 4.39 Experimental C, 75.32; H, 5.43; n, 4.38
47		Light brown needles [EtOH] mp, 173~175°C Elemental analysis $C_{19}H_{15}FN_2O_3 \cdot HCl$ Theoretical C, 60.89; H, 4.30; N, 7.47 Experimental C, 60.84; H, 4.26; N, 7.45
48		Colorless crystals [AcOEt] mp, 91~92°C Elemental analysis $C_{17}H_{18}FNO_4$ Theoretical C, 63.94; H, 5.68; N, 4.39 Experimental C, 63.71; H, 5.59; N, 4.35
49		Light yellow-brown prisms [iso-Pr_2O] mp, 81.5~82°C Elemental analysis $C_{18}H_{21}FN_2O_3$ Theoretical C, 65.05; H, 6.37; N, 8.43 Experimental C, 64.93; H, 6.37; N, 8.46
50		Yellow-brown crystals [iso-Pr_2O] mp, 74~75°C Elemental analysis $C_{19}H_{23}FN_2O_3$ Theoretical C, 65.88; H, 6.69; N, 8.09 Experimental C, 65.86; H, 6.67; N, 7.98

Reference example	Chemical formula	Form and physical properties [Recrystallization solvent]
51		Red-brown liquid NMR(DMSO-d_6) δ ppm: 1.52 (2H, quin, J=7Hz), 1.70 (2H, quin, J=7Hz), 2.11 (6H, s), 2.23 (2H, t, J=7Hz), 3.99 (2H, t, J=7Hz), 5.14 (2H, s), 7.06 (1H, t, J=9Hz), 7.14 (1H, dd, J=9, 1Hz), 7.30-7.42 (6H, m), 9.62 (1H, brs) IR ν (liq.) cm^{-1}: 1730
52		Brown liquid NMR($CDCl_3$) δ ppm: 2.25 (6H, s), 2.47 (2H, t, J=7.5Hz), 2.81 (3H, s), 3.18 (2H, t, J=7.5Hz), 5.19 (2H, s), 6.59 (1H, brs), 6.86 (1H, t, J=9.5Hz), 6.94 (1H, d, J=9.5Hz), 7.20-7.25 (1H, m), 7.30-7.45 (5H, m) IR ν (liq.) cm^{-1}: 1732, 3180, 3320 MS(m/z): 345 (M^+)
53		Colorless needles [iso-PrOH] mp, 100~100.5°C Elemental analysis $C_{18}H_{19}NO_2$ Theoretical C, 76.84; H, 6.81; N, 4.98 Experimental C, 76.85; H, 7.07; N, 4.98

Reference Example 54: N,N'-di-tert-Butoxycarbonyl-3-fluoro-4-(piperazin-1-yl)aniline

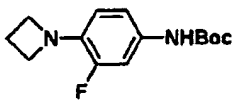
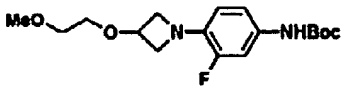
10 mL of methanol solution containing 2.00 g of 3-fluoro-4-(piperazin-1-yl)aniline was added dropwise to 10 mL of a methanol solution containing 5.56 g of di-tert-butyl dicarbonate while stirring at room temperature, and the solution was stirred overnight at room temperature. The precipitated crystals were filtered and washed with ethanol to obtain 3.12 g of yellow crystals. The material was recrystallized from ethyl acetate to obtain light yellow crystals with a melting point of 194-195°C.

Elemental analysis $C_{20}H_{30}FN_3O_4$

Theoretical C 60.74; H 7.65; N 10.63

Experimental C 60.47; H 7.93; N 10.53

The compounds of Reference Examples 55 and 56 were obtained in the same manner as in Reference Example 54.

Reference example	Chemical formula	Form and physical properties [Recrystallization solvent]
55		Brown liquid NMR(DMSO-d_6) δ ppm: 1.45 (9H, s), 2.24 (2H, quin, J=7.5Hz), 3.80 (4H, td, J=7.5, 2Hz), 6.42 (1H, t, J=8.5Hz), 7.02 (1H, dd, J=8.5, 2Hz), 7.21 (1H, dd, J=14.5, 2Hz), 9.01 (1H, brs) IR ν (liq.) cm^{-1}: 1704, 3332
56		Brown liquid NMR(DMSO-d_6) δ ppm: 1.45 (9H, s), 3.26 (3H, s), 3.44 (2H, t, J=4.5Hz), 3.52 (2H, t, J=4.5Hz), 3.55-3.60 (2H, m), 4.00-4.10 (2H, m), 4.35-4.40 (1H, m), 6.46 (1H, t, J=8.5Hz), 7.04 (1H, dd, J=8.5, 2Hz), 7.22 (1H, dd, J=15, 2Hz), 9.03 (1H, brs) IR ν (liq.) cm^{-1}: 1724, 3328 MS(m/z): 340 (M^+)

Reference Example 57: (R)-5-Hydroxymethyl-2-oxo-3-[4-(thiomorpholin-4-yl)phenyl]oxazolidine

50 mL of an n-hexane solution containing n-butyl lithium (1.63 mol/L) was added dropwise to 250 mL of an anhydrous tetrahydrofuran solution containing 25.0 g of N-benzyloxycarbonyl-4-(thiomorpholin-4-yl)aniline under a flow of nitrogen while stirring at -78°C, and after completion of dropwise addition, the solution was stirred for 1 hour at the same temperature. 11.5 mL of (R)-(-)-glycidylbutyrate was added dropwise to the mixed solution and upon completion of dropwise addition, stirring was carried out for 1 hour at the same temperature and for 23 hours at room temperature. 250 mL of 10% ammonium chloride aqueous solution was added to the reaction solution, and extraction was performed with ethyl acetate. The extract was then washed in sequence with water and saturated sodium chloride, and after drying on anhydrous sodium sulfate, the solvent was evaporated off under reduced pressure. The residue was then washed with diisopropyl ether to obtain 18.8 g of gray-brown crystals. The crystals were recrystallized from ethyl acetate to obtain colorless crystals with a melting point of 126.5-127.5°C.

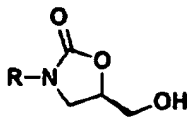
Elemental analysis: $C_{14}H_{18}N_2O_3S$

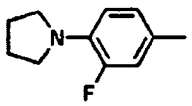
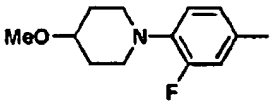
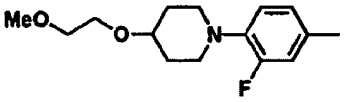
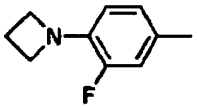
Theoretical C 57.12; H 6.16; N 9.52

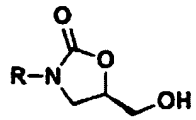
Experimental C 56.85; H 6.13; N 9.25

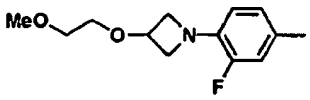
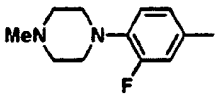
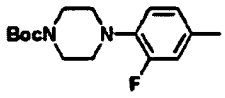
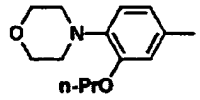
Optical Rotation $[\alpha]_D^{20}$: -40.9° (c=0.1, DMSO)

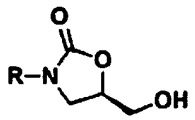
The compounds of Reference Example 58-79 were obtained in the same manner as in Reference Example 57.

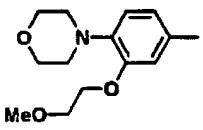
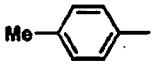
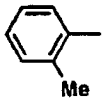
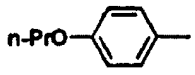


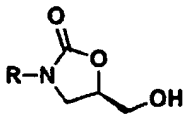
Reference example	R	Form and physical properties [Recrystallization solvent]
58		Light purple needles [EtOH] mp, 178~179°C Elemental analysis $C_{14}H_{17}FN_2O_3$ Theoretical C, 59.99; H, 6.11; N, 9.99 Experimental C, 59.97; H, 6.06; N, 9.98 Optical Rotation $[\alpha]_D^{20}$-54.9° (c=0.1, DMSO)
59		Light purple crystals [AcOEt] mp, 139.5~141°C Elemental analysis $C_{16}H_{21}FN_2O_4$ Theoretical C, 59.25; H, 6.53; N, 8.64 Experimental C, 58.95; H, 6.46; N, 8.39 Optical Rotation $[\alpha]_D^{20}$-43.1° (c=0.1, DMSO)
60		Colorless crystals [AcOEt] mp, 94.5~96°C Elemental analysis $C_{18}H_{25}FN_2O_5$ Theoretical C, 58.68; H, 6.84; N, 7.60 Experimental C, 58.41; H, 7.11; N, 7.56 Optical Rotation $[\alpha]_D^{20}$-37.9° (c=0.1, DMSO)
61		Light brown crystals NMR(DMSO-d_6) δ ppm: 2.27 (2H, quin, J=7.5Hz), 3.50-3.60 (1H, m), 3.60-3.70 (1H, m), 3.75 (1H, dd, J=8.5, 6Hz), 3.85 (4H, td, J=7.5, 2Hz), 4.00 (1H, t, J=9Hz), 4.60-4.70 (1H, m), 5.07 (1H, t, J=6Hz), 6.53 (1H, dd, J=10, 8.5Hz), 7.11 (1H, dd, J=8.5, 2.5Hz), 7.37 (1H, dd, J=15, 2.5Hz) IR ν (liq.) cm^{-1}: 1702, 3844 MS(m/z): 266 (M^+) Optical Rotation $[\alpha]_D^{20}$-44.0° (c=0.1, DMSO)

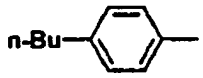
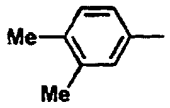
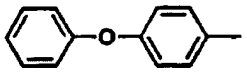
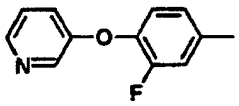
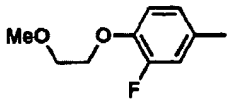
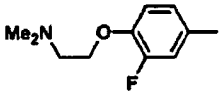


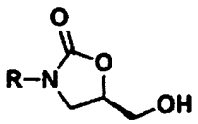
Reference example	R	Form and physical properties [Recrystallization solvent]
62		Colorless needles [AcOEt] mp, 113~114°C Elemental analysis $C_{16}H_{21}FN_2O_5$ Theoretical C, 56.46; H, 6.22; N, 8.23 Experimental C, 56.30; H, 6.33; N, 8.24 Optical Rotation $[\alpha]_D^{20}$-41.2° (c=0.1, DMSO)
63		Colorless prisms [iso-PrOH] mp, 150~151°C Elemental analysis $C_{15}H_{20}FN_3O_3$ Theoretical C, 58.24; H, 6.52; N, 13.58 Experimental C, 58.33; H, 6.31; N, 13.56 Optical Rotation $[\alpha]_D^{20}$-38.9° (c=0.1, DMSO)
64		Light brown crystals [iso-PrOH] mp, 130~132°C Elemental analysis $C_{19}H_{26}FN_3O_5$ Theoretical C, 57.71; H, 6.63; N, 10.63 Experimental C, 57.55; H, 6.87; N, 10.57 Optical Rotation $[\alpha]_D^{20}$-36.0° (c=0.1, DMSO)
65		Light brown crystals NMR(DMSO-d_6) δ ppm: 1.01 (3H, t, J=7.5Hz), 1.76 (2H, sex, J=7.5Hz), 2.95 (4H, t, J=5Hz), 3.53-3.59 (1H, m), 3.62-3.68 (1H, m), 3.72 (4H, t, J=5Hz), 3.79 (1H, dd, J=9, 6.5Hz), 3.93 (2H, t, J=7.5Hz), 4.03 (1H, t, J=9Hz), 4.61-4.68 (1H, m), 5.07 (1H, t, J=5.5Hz), 6.87 (1H, d, J=9Hz), 6.93 (1H, dd, J=9, 2.5Hz), 7.29 (1H, d, J=2.5Hz) IR ν (liq.) cm^{-1}: 1738, 3396 MS(m/z): 336 (M^+) Optical Rotation $[\alpha]_D^{20}$-35.1° (c=0.1, DMSO)

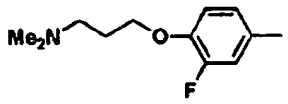
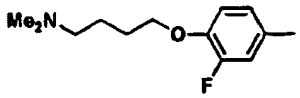
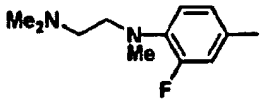
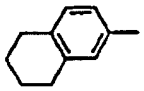


Reference example	R	Form and physical properties [Recrystallization solvent]
66		Colorless crystals NMR(DMSO-d_6) δ ppm: 2.96 (4H, t, J=5Hz), 3.33 (3H, s), 3.53-3.60 (1H, m), 3.62-3.70 (1H, m), 3.68 (2H, t, J=5Hz), 3.71 (4H, t, J=5Hz), 3.80 (1H, dd, J=9, 6.5Hz), 4.04 (1H, t, J=9Hz), 4.09 (2H, t, J=5Hz), 4.61-4.68 (1H, m), 5.08 (1H, t, J=5.5Hz), 6.87 (1H, d, J=8.5Hz), 6.98 (1H, dd, J=8.5, 2.5Hz), 7.28 (1H, d, J=2.5Hz) IR ν (liq.) cm^{-1}: 1744, 3440 MS(m/z): 352 Optical Rotation $[\alpha]_D^{20}$-36.0° (c=0.1, DMSO)
67		Light yellow crystals [EtOH] mp, 127.5~128.5°C Elemental analysis $C_{11}H_{13}NO_3$ Theoretical C, 63.76; H, 6.32; N, 6.76 Experimental C, 63.59; H, 6.39; N, 6.78 Optical Rotation $[\alpha]_D^{20}$-55.0° (c=0.1, DMSO)
68		Colorless prisms [AcOEt-iso-Pr2O] mp, 87~88°C Elemental analysis $C_{11}H_{13}NO_3$ Theoretical C, 63.76; H, 6.32; N, 6.76 Experimental C, 63.60; H, 6.31; N, 6.75 Optical Rotation $[\alpha]_D^{20}$-40.3° (c=0.5, DMSO)
69		Colorless crystals [AcOet] mp, 157~158.5°C Elemental analysis $C_{13}H_{17}NO_4$ Theoretical C, 62.14; H, 6.82; N, 5.57 Experimental C, 61.99; H, 6.95; N, 5.55 Optical Rotation $[\alpha]_D^{20}$-41.1° (c=0.1, DMSO)



Reference example	R	Form and physical properties [Recrystallization solvent]
70		Colorless crystals [AcOEt] mp, 140.5~142°C Elemental analysis $C_{14}H_{19}NO_3$ Theoretical C, 67.45; H, 7.68; N, 5.62 Experimental C, 67.35; H, 7.70; N, 5.65 Optical Rotation $[\alpha]_D^{20}$-49.0° (c=0.1, DMSO)
71		Colorless prisms [EtOH] mp, 150~151°C Elemental analysis $C_{12}H_{15}NO_3$ Theoretical C, 65.14; H, 6.83; N, 6.33 Experimental C, 65.01; H, 6.64; N, 6.28 Optical Rotation $[\alpha]_D^{20}$-45.9° (c=0.1, DMSO)
72		Colorless needles [AcOEt-n-Hexane] mp, 93~94°C Elemental analysis $C_{16}H_{15}NO_4$ Theoretical C, 67.36; H, 5.30; N, 4.91 Experimental C, 67.28; H, 5.30; N, 4.92 Optical Rotation $[\alpha]_D^{20}$-46.4° (c=0.4, MeOH)
73		Light orange crystals [AcOEt] mp, 137~139°C Elemental analysis $C_{15}H_{13}FN_2O_4$ Theoretical C, 59.21; H, 4.31; N, 9.21 Experimental C, 59.08; H, 4.48; N, 9.05 Optical Rotation $[\alpha]_D^{20}$-39.9° (c=0.1, DMSO)
74		Light brown needles [iso-PrOH] mp, 119~120°C Elemental analysis $C_{13}H_{16}FNO_5$ Theoretical C, 54.73; H, 5.65; N, 4.91 Experimental C, 54.58; H, 5.55; N, 4.89 Optical Rotation $[\alpha]_D^{20}$-40.9° (c=0.1, DMSO)
75		Colorless prisms [AcOEt] mp, 127~128°C Elemental analysis $C_{14}H_{19}FN_2O_4$ Theoretical C, 56.37; H, 6.42; N, 9.39 Experimental C, 56.32; H, 6.22; N, 9.37 Optical Rotation $[\alpha]_D^{20}$-42.2° (c=0.1, DMSO)



Reference example	R	Form and physical properties [Recrystallization solvent]
76		Light yellow-brown prisms [AcOEt] mp, 80~81°C Elemental analysis $C_{15}H_{21}FN_2O_4$ Theoretical C, 57.68; H, 6.78: N, 8.97 Experimental C, 57.59; H, 6.74; N, 8.95 Optical Rotation $[\alpha]_D^{20}$-38.2° (c=0.1, DMSO)
77		Colorless needles [iso-PrOH-iso-Pr_2O] mp, 66~66.5°C Elemental analysis $C_{16}H_{23}FN_2O_4$ Theoretical C, 58.88; H, 7.10; N, 8.58 Experimental C, 58.64; H, 6.81; N, 8.49 Optical Rotation $[\alpha]_D^{20}$-38.8° (c=0.1, DMSO)
78		Light yellow cylinders [iso-PrOH] mp, 111~112°C Elemental analysis $C_{15}H_{22}FN_3O_3$ Theoretical C, 57.86; H, 7.12; N, 13.50 Experimental C, 57.96; H, 7.12; N, 13.40 Optical Rotation $[\alpha]_D^{20}$-40.0° (c=0.1, DMSO)
79		Colorless Prisms [AcOEt] mp, 145.5~146.5°C Elemental analysis $C_{14}H_{17}NO_3$ Theoretical C, 68.00; H, 6.93; N, 5.66 Experimental C, 67.88; H, 7.23; N, 5.68 Optical Rotation $[\alpha]_D^{20}$-51.1° (c=0.1, DMSO)

Reference Example 80: (R)-5-Methanesulfonyloxymethyl-2-oxo-3-[4-(thiomorpholin-4-yl)phenyl]oxazolidine

3.20 mL of methanesulfonyl chloride was added dropwise to 200 mL of a dichloromethane solution containing 10.0 g of (R)-5-hydroxymethyl-2-oxo-3-[4-(thiomorpholin-4-yl)phenyl]oxazolidine and 10.5 mL of triethylamine while stirring and chilling on ice, whereupon the solution was stirred for 2 hours at room temperature. Water was added to the reaction solution and extraction was performed with dichloromethane. The extract was washed in sequence with water and saturated sodium chloride aqueous solution, and after drying with anhydrous sodium sulfate the solvent was evaporated off under reduced pressure. The residue was washed with diisopropyl ether to obtain 11.5 g of gray-brown crystals, which were recrystallized form ethyl acetate to obtain colorless prisms with a melting point of 174.5-175.5°C.

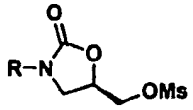
Elemental analysis $C_{15}H_{20}N_2O_5S_2$

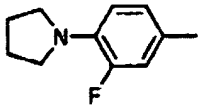
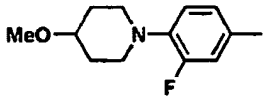
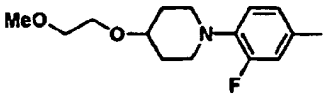
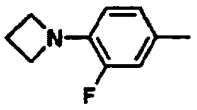
Theoretical: C 48.37; H 5.41; N 7.52

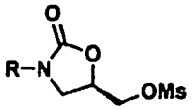
Experimental: C 48.41; H 5.33; N 7.36

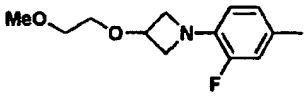
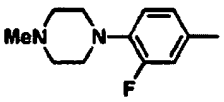
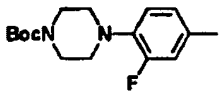
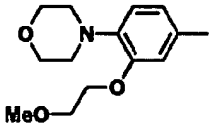
Optical Rotation $[\alpha]_D^{20}$: -54.2° (c=0.1, DMSO)

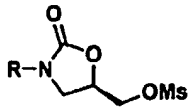
The compounds of Reference Examples 81-104 were obtained in the same manner as in Reference Example 80.

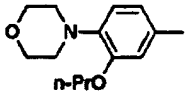
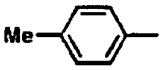
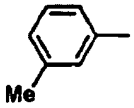
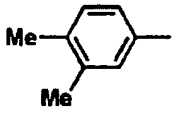


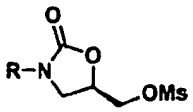
Reference example	R	Form and physical properties [Recrystallization solvent]
81		Colorless crystals [AcOEt-iso-Pr_2O] mp, 111~112°C Elemental analysis $C_{15}H_{19}FN_2O_5S$ Theoretical C, 50.27; H, 5.34; N, 7.82 Experimental C, 50.10; H, 5.30; N, 7.73 Optical Rotation $[\alpha]_D^{20}$-50.1° (c=0.1, DMSO)
82		Colorless prisms [AcOEt] mp, 124.5~125.5°C Elemental analysis $C_{17}H_{23}FN_2O_6S$ Theoretical C, 50.74; H, 5.76; N, 6.96 Experimental C, 50.50; H, 5.66; N, 6.87 Optical Rotation $[\alpha]_D^{20}$-49.9° (c=0.1, DMSO)
83		Light brown needles [AcOEt] mp, 124~124.5°C Elemental analysis $C_{19}H_{27}FN_2O_7S$ Theoretical C, 51.11; H, 6.10; N, 6.27 Experimental C, 50.82; H, 6.34; N, 6.25 Optical Rotation $[\alpha]_D^{20}$-47.8° (c=0.1, DMSO)
84		Light brown needles [iso-PrOH] mp, 139.5~141.5°C Elemental analysis $C_{14}H_{17}FN_2O_5S$ Theoretical C, 48.83; H, 4.98; N, 8.13 Experimental C, 48.67; H, 4.88; N, 7.97 Optical Rotation $[\alpha]_D^{20}$-55.0° (c=0.1, DMSO)

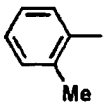
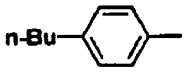
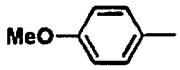
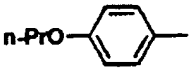
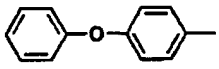


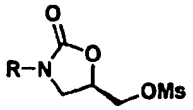
Reference example	R	Form and physical properties [Recrystallization solvent]
85		Brown liquid NMR(DMSO-d_6) δ ppm: 3.22 (3H, s), 3.26 (3H, s), 3.45 (2H, t, J=5Hz), 3.53 (2H, t, J=5Hz), 3.60-3.70 (2H, m), 3.77 (1H, dd, J=9.5, 6.5Hz), 4.10-4.15 (3H, m), 4.35-4.45 (1H, m), 4.44 (1H, dd, J=11.5, 5.5Hz), 4.49 (1H, dd, J=11.5, 3Hz), 4.90-5.00 (1H, m), 6.58 (1H, mt, J=9Hz), 7.12 (1H, dd, J=9, 2.5Hz), 7.37 (1H, dd, J=14.5, 2.5Hz) IR ν (liq.) cm^{-1}: 1754 MS(m/z): 418 (M^+) Optical Rotation $[\alpha]_D^{20}$-45.7° (c=0.1, DMSO)
86		Colorless prisms [AcOEt] mp, 159.5~160.5°C Elemental analysis $C_{16}H_{22}FN_3O_5S$ Theoretical C, 49.60; H, 5.72; N, 10.85 Experimental C, 49.58; H, 5.46; N, 10.75 Optical Rotation $[\alpha]_D^{20}$-49.0° (c=0.1, DMSO)
87		Colorless prisms [MeOH] mp, 182.5~183.5°C Elemental analysis $C_{20}H_{28}FN_3O_7S$ Theoretical C, 50.73; H, 5.96; N, 8.87 Experimental C, 50.63; H, 6.11; N, 8.88 Optical Rotation $[\alpha]_D^{20}$-46.0° (c=0.1, DMSO)
88		Colorless prisms [iso-PrOH] mp, 100.5~101.5°C Elemental analysis $C_{18}H_{26}N_2O_8S$ Theoretical C, 50.22; H, 6.09; N, 6.51 Experimental C, 50.12; H, 6.00; N, 6.39 Optical Rotation $[\alpha]_D^{20}$-44.2° (c=0.1, DMSO)

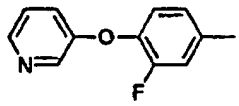
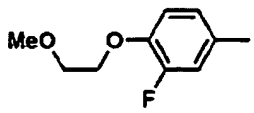
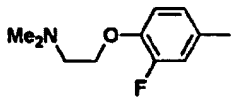
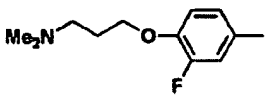


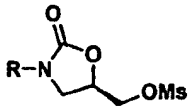
Reference example	R	Form and physical properties [Recrystallization solvent]
89		Colorless liquid NMR(DMSO-d_6) δ ppm: 1.01 (3H, t, J=7.5Hz), 1.76 (2H, sex, J=7.5Hz), 2.96 (4H, t, J=5Hz), 3,23 (3H, s), 3.72 (4H, t, J=5Hz), 3.80 (1H, dd, J=9, 6.5Hz), 3.93 (2H, t, J=7.5Hz), 4.15 (1H, t, J=9Hz), 4.44 (1H, dd, J=11.5, 5Hz), 4.50 (1H, dd, J=11.5, 3Hz), 4.93-5.00 (1H, m), 6.88 (1H, d, J=8.5Hz), 6.93 (1H, dd, J=8.5, 2.5Hz), 7.27 (1H, d, J=2.5Hz) IR ν (liq.) cm^{-1}: 1754 MS(m/z): 414 (M^+) Optical Rotation $[\alpha]_D^{20}$-41.9° (c=0.1, DMSO)
90		Light brown crystals [iso-PrOH] mp, 128~130°C Elemental analysis $C_{12}H_{15}NO_5S$ Theoretical C, 50.52; H, 5.30; N, 4.91 Experimental C, 50.23; H, 5.30; N, 4.83 Optical Rotation $[\alpha]_D^{20}$-54.0° (c=0.1, DMSO)
91		Light brown liquid NMR(DMSO-d_6) δ ppm: 2.32 (3H, s), 3.23 (3H, s), 3.83 (1H, dd, J=9, 6Hz), 4.18 (1H, t, J=9Hz), 4.45 (1H,dd, J=11.5, 5.5Hz), 4.51 (1H, dd, J=11.5, 3Hz), 4.96-5.01 (1H, m), 6.96 (1H, d, J=7.5Hz), 7.27 (1H, t, J=7.5Hz), 7.30-7.40 (2H, m) IR ν (liq.) cm^{-1}: 1754 MS(m/z): 285 (M^+) Optical Rotation $[\alpha]_D^{20}$-55.8° (c=0.1, DMSO)
92		Light yellow prisms [iso-PrOH] mp, 113~113.5°C Elemental analysis $C_{13}H_{17}NO_5S$ Theoretical C, 52.16; H, 5.72; N, 4.68 Experimental C, 51.91; H, 5.56; N, 4.63 Optical Rotation $[\alpha]_D^{20}$-52.9° (c=0.1, DMSO)

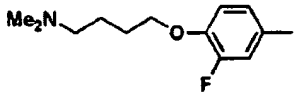
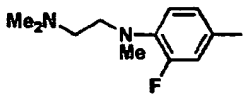
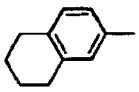


Reference example	R	Form and physical properties [Recrystallization solvent]
93		Light yellow liquid NMR ($CDCl_3$) δ ppm: 2.32 (3H, s), 3.14 (3H, s), 3.85 (1H, dd, J=9, 5.5Hz), 4.07 (1H, t, J=9Hz), 4.32 (1H, dd, J=11.5, 4.5Hz), 4.53 (1H, dd, J=11.5, 3.5Hz), 4.90-5.00 (1H, m), 7.20-7.40 (4H, m) IR ν (liq.) cm^{-1}: 1754 MS (m/z): 285 (M^+) Optical Rotation $[\alpha]_D^{20}$-57.6° (c=0.1, MeOH)
94		Colorless crystals [MeOH] mp, 109~110.5°C Elemental analysis $C_{15}H_{21}NO_5S$ Theoretical C, 55.03; H, 6.47; N, 4.28 Experimental C, 54.86; H, 6.25; N, 4.36 Optical Rotation $[\alpha]_D^{20}$-52.9° (c=0.1, DMSO)
95		Colorless scales [MeOH] mp, 149~150°C Elemental analysis $C_{12}H_{15}NO_6S$ Theoretical C, 47.83; H, 5.02; N, 4.65 Experimental C, 48.02; H, 4.95; N, 4.72 Optical Rotation $[\alpha]_D^{20}$-57.5° (c=0.5, DMSO)
96		Colorless needles [iso-PrOH] mp, 85.5~87.5°C Elemental analysis $C_{14}H_{19}NO_6S$ Theoretical C, 51.05; H, 5.81; N, 4.25 Experimental C, 50.77; H, 5.93; N, 4.30 Optical Rotation $[\alpha]_D^{20}$-48.9° (c=0.1, DMSO)
97		Light brown scales [AcOEt] mp, 106~107°C Elemental analysis $C_{17}H_{17}NO_6S$ Theoretical C, 56.19; H, 4.72; N, 3.85 Experimental C, 55.97; H, 4.72; N, 3.84 Optical Rotation $[\alpha]_D^{20}$-59.3° (c=0.5, MeOH)



Reference example	R	Form and physical properties [Recrystallization solvent]
98		Colorless platelets [EtOH] mp, 120~121°C Elemental analysis $C_{16}H_{15}FN_2O_6S$ Theoretical C, 50.26; H, 3.95; N, 7.33 Experimental C, 50.24; H, 3.93; N, 7.27 Optical Rotation $[\alpha]_D^{20}$-51.1° (c=0.1, DMSO)
99		Colorless crystals [EtOH] mp, 72.5~74°C Elemental analysis $C_{14}H_{18}FNO_7S$ Theoretical C, 46.28; H, 4.99; N, 3.85 Experimental C, 46.22; H, 4.95; N, 3.83 Optical Rotation $[\alpha]_D^{20}$-51.2° (c=0.1, DMSO)
100		Colorless crystals [iso-PrOH-iso-Pr_2O] mp, 61.5~62.5°C Elemental analysis $C_{15}H_{21}FN_2O_6S \cdot 1/4H_2O$ Theoretical C, 47.30; H, 5.69; N, 7.35 Experimental C, 47.00; H, 5.44; N, 7.20 Optical Rotation $[\alpha]_D^{20}$-45.9° (c=0.1, DMSO)
101		Yellow-brown liquid NMR (DMSO-d_6) δ ppm: 1.84 (2H, quin, J=6.5Hz), 2.15 (6H, 2), 2.37 (2H, t, J=6.5Hz), 3.23 (3H, s), 3.80 (1H, dd, J=9, 6Hz), 4.06 (2H, t, J=6.5Hz), 4.15 (1H, t, J=9Hz), 4.45 (1H, dd, J=11.5, 4.5Hz), 4.51 (1H, dd, J=11.5, 3Hz), 4.95-5.00 (1H, m), 7.15-7.25 (2H, m), 7.52 (1H, dd, J=13.5, 2.5Hz) IR ν (liq.) cm^{-1}: 1754 MS (m/z): 390 (M^+) Optical Rotation $[\alpha]_D^{20}$-48.9° (c=0.1, DMSO)



Reference example	R	Form and physical properties [Recrystallization solvent]
102		Light yellow-brown liquid NMR (DMSO-d_6) δ ppm: 1.53 (2H, quin, J=7Hz), 1.72 (2H, quin, J=7Hz), 2.12 (6H, 2), 2.24 (2H, t, J=7Hz), 3.23 (3H, 2), 3.80 (1H, dd, J=9, 6Hz), 4.04 (2H, t, J=7Hz), 4.15 (1H, t, J=9Hz), 4.45 (1H, dd, J=11.5, 5.5Hz), 4.49 (1H, dd, J=11.5, 3Hz), 4.95-5.00 (1H, m), 7.15-7.25 (1H, m), 7.31-7.38 (1H, m), 7.49-7.54 (1H, m) IR ν (liq.) cm^{-1}: 1756 Optical Rotation $[\alpha]_D^{20}$-14.0° (c=0.1, DMSO)
103		Light yellow prisms [EtOH] (hydrochloride) mp, 143~144.5°C Elemental analysis $C_{16}H_{24}FN_3O_5S \cdot HCl$ Theoretical C, 45.12; H, 5.92; N, 9.87 Experimental C, 44.99; H, 5.88; N, 9.72 Optical Rotation $[\alpha]_D^{20}$-41.1° (c=0.1, DMSO)
104		Colorless crystals [iso-PrOH] mp, 100.5~102.5°C Elemental analysis $C_{15}H_{19}NO_5S$ Theoretical C, 55.37; H, 5.89; N, 4.30 Experimental C, 55.11; H, 6.02; N, 4.27 Optical Rotation $[\alpha]_D^{20}$-58.1° (c=0.1, DMSO)

Reference Example 105: (R)-5-Azidomethyl-2-oxo-3-[4-(thiomorpholin-4-yl)phenyl]oxazolidine

110 mL of an anhydrous N,N-dimethylformamide suspension containing 11.5 g of (R)-5-methanesulfonyloxymethyl-2-oxo-3-[4-(thiomorpholin-4-yl)phenyl]oxazolidine and 8.35 g of sodium azide was stirred for 5 h at 65°C. After chilling, water was added to the reaction solution, and extraction was performed with ethyl acetate. The extract was then washed in sequence with water and saturated sodium chloride aqueous solution, and after drying on anhydrous sodium sulfate, the solvent was evaporated off under reduced pressure. The residue was then washed with diisopropyl ether to obtain 8.85 g of gray-brown crystals, which were recrystallized from ethyl acetate to obtain colorless crystals with a melting point of 110-111°C.

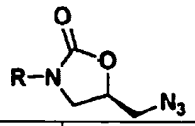
Elemental analysis $C_{14}H_{17}N_5O_2S$

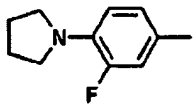
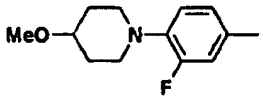
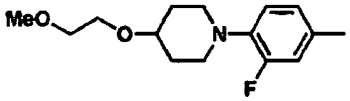
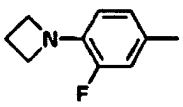
Theoretical: C 52.65; H 5.37; N 21.93

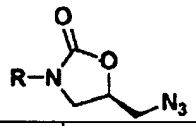
Experimental: 52.47; H 5.35; N 21.65

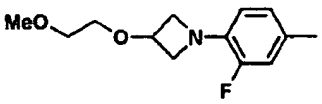
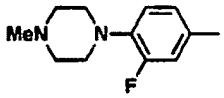
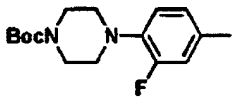
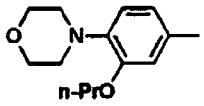
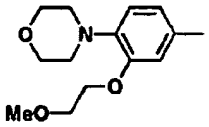
Optical Rotation $[\alpha]_D^{20}$: -124.4° (c=0.1, DMSO)

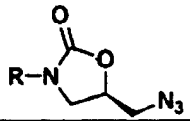
The compounds of Reference Example 106-129 were obtained in the same manner as in Reference Example 105.

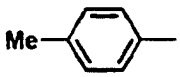
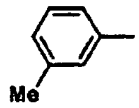
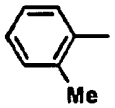
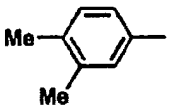


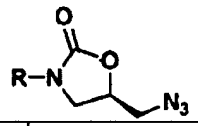
Reference example	R	Form and physical properties [Recrystallization solvent]
106		Colorless crystals [AcOEt] mp, 109~109.5°C Elemental analysis $C_{14}H_{16}FN_5O_2$ Theoretical C, 55.08; H, 5.28; N, 22.94 Experimental C, 54.88; H, 5.12; N, 22.70 Optical Rotation $[\alpha]_D^{20}$-136.4° (c=0.1, DMSO)
107		Colorless needles [AcOEt-iso-Pr_2O] mp, 89~90°C Elemental analysis $C_{16}H_{20}FN_5O_3$ Theoretical C, 55.01; H, 5.77; N, 20.05 Experimental C, 54.83; H, 5.72; N, 19.88 Optical Rotation $[\alpha]_D^{20}$-118.5° (c=0.1, DMSO)
108		Light brown liquid NMR (DMSO-d_6) δ ppm: 1.55-1.65 (2H, m), 1.90-2.00 (2H, m), 2.75-2.80 (2H, m), 3.15-3.25 (2H, m), 3.27 (3H, s), 3.40-3.50 (1H, m), 3.45 (2H, t, J=5Hz), 3.56 (2H, t, J=5Hz), 3.67 (1H, dd, J=13.5, 6Hz), 3.70-3.80 (2H, m), 4.10 (1H, t, J=9Hz), 4.80-4.90 (1H, m), 7.06 (1H, t, J=9Hz), 7.17 (1H, dd, J=9, 2.5Hz), 7.45 (1h, dd, J=15, 2.5Hz) IR ν (liq.) cm^{-1}: 1756, 2112 MS (m/z): 393 (M^+) Optical Rotation $[\alpha]_D^{20}$-100.3° (c=0.1, DMSO)
109		Brown liquid NMR (DMSO-d_6) δ ppm: 2.28 (2H, quin, J=7.5Hz), 3.60-3.75 (3H, m), 3.86 (4H, td, J=7.5, 2.5Hz), 4.07 (1H, t, J=9Hz), 4.80-4.90 (1H, m), 6.54 (1H, dd, J=10.5, 8.5Hz), 7.11 (1H, dd, J=8.5, 2.5Hz), 7.35 (1H, dd, J=14.5, 2.5Hz) IR ν (liq.) cm^{-1}: 1732, 2116 MS (m/z): 291 (M^+) Optical Rotation $[\alpha]_D^{20}$-90.8° (c=0.1, DMSO)

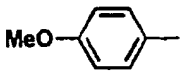
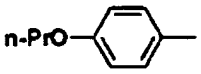
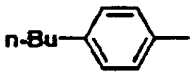
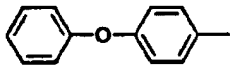


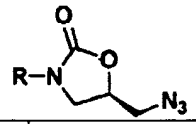
Reference example	R	Form and physical properties [Recrystallization solvent]
110		Brown liquid NMR (DMSO-d_6) δ ppm: 3.26 (3H, s), 3.45 (2H, t, J=4.5Hz), 3.53 (2H, t, J=4.5Hz), 3.60-3.75 (5H, m), 4.08 (1H, t, J=9Hz), 4.05-4.15 (2H, m), 4.35-4.45 (1H, m), 4.80-4.90 (1H, m), 6.58 (1H, t, J=8.5Hz), 7.12 (1H, dd, J=8.5, 2Hz), 7.38 (1H, dd, J=14.5, 2Hz) IR ν (liq.) cm^{-1}: 1752, 2112 MS (m/z): 365 (M^+) Optical Rotation $[\alpha]_D^{20}$-91.4° (c=0.1, DMSO)
111		Colorless scales [iso-PrOH] mp, 106.5~107°C Elemental analysis $C_{15}H_{19}FN_6O_2$ Theoretical C, 53.88; H, 5.73; N, 25.14 Experimental C, 53.88; H, 5.63; N, 25.14 Optical Rotation $[\alpha]_D^{20}$-118.5° (c=0.1, DMSO)
112		Light brown needles [iso-PrOH] mp, 112~113°C Elemental analysis $C_{19}H_{25}FN_6O_4$ Theoretical C, 54.28; H, 5.99; N, 19.99 Experimental C, 54.20; H, 6.09; N, 20.07 Optical Rotation $[\alpha]_D^{20}$-101.9° (c=0.1, DMSO)
113		Light brown needles [iso-PrOH] mp, 86.5~87°C Elemental analysis $C_{17}H_{23}N_5O_4$ Theoretical C, 56.50; H, 6.41; N, 19.38 Experimental C, 56.70; H, 6.57; N, 19.41 Optical Rotation $[\alpha]_D^{20}$-108.6° (c=0.1, DMSO)
114		Brown liquid NMR (DMSO-d_6) δ ppm: 2.96 (4H, t, J=5Hz), 3.33 (3H, s), 3.64-3.79 (9H, m), 4.08-4.14 (3H, m), 4.82-4.88 (1H, m), 6.88 (1H, d, J=8.5Hz), 6.98 (1H, dd, J=8.5, 2.5Hz), 7.26 (1H, d, J=2.5Hz) IR ν (liq.) cm^{-1}: 1754, 2112 MS (m/z): 377 (M^+) Optical Rotation $[\alpha]_D^{20}$-98.0° (c=0.1, DMSO)

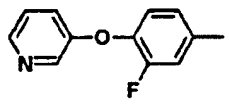
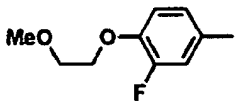
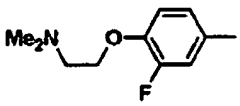
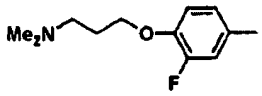


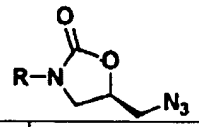
Reference example	R	Form and physical properties [Recrystallization solvent]
115		Red-brown liquid NMR ($CDCl_3$) δ ppm: 2.33 (3H, s), 3.59 (1H, dd, J=13.5, 4.5Hz), 3.68 (1H, dd, J=13.5, 4.5Hz), 3.84 (1H, dd, J=9, 6Hz), 4.08 (1H, t, J=9Hz), 4.74-4.80 (1H, m), 7.18 (2H, d, J=8Hz), 7.41 (2H, d, J=8Hz) IR ν (liq.) cm^{-1}: 1754, 2112 MS (m/z): 232 (M^+) Optical Rotation $[\alpha]_D^{20}$-119.1° (c=0.1, DMSO)
116		Colorless crystals NMR (DMSO-d_6) δ ppm: 2.32 (3H, s), 3.68 (1H, dd, J=13.5, 6Hz), 3.70-3.80 (2H, m), 4.13 (1H, t, J=9Hz), 4.80-4.90 (1H, m), 6.95 (1H, d, J=8Hz), 7.26 (1H, t, J=8Hz), 7.30-7.40 (2H, m) IR ν (KBr) cm^{-1}: 1736, 2116 MS (m/z): 232 (M^+) Optical Rotation $[\alpha]_D^{20}$-148.1° (c=0.1, DMSO)
117		Light yellow liquid NMR ($CDCl_3$) δ ppm: 2.33 (3H, s), 3.58 (1H, dd, J=13.5, 4.5Hz), 3.70-3.80 (2H, m), 3.99 (1H, t, J=9Hz), 4.80-4.90 (1H, m), 7.20-7.40 (4H, m) IR ν (liq.) cm^{-1}: 1754, 2112 MS (m/z): 232 (M^+) Optical Rotation $[\alpha]_D^{20}$-130.1° (c=0.5, MeOH)
118		Light brown crystals [iso-Pr_2O] mp, 85~85.5°C Elemental analysis $C_{12}H_{14}N_4O_2$ Theoretical C, 58.53; H, 5.73; N, 22.75 Experimental C, 58.30; H, 5.59; N, 22.46 Optical Rotation $[\alpha]_D^{20}$-140.4° (c=0.1, DMSO)

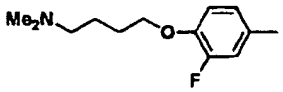
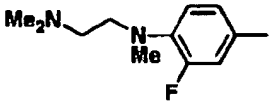
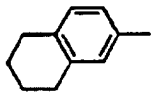


Reference example	R	Form and physical properties [Recrystallization solvent]
119		Colorless prisms [AcOEt-n-Hexane] mp, 80~81°C Elemental analysis $C_{11}H_{12}N_4O_3$ Theoretical C, 53.22; 4.87; N, 22.57 Experimental C, 53.28; H, 4.96; N, 22.60 Optical Rotation $[\alpha]_D^{20}$-158.5° (c=0.5, MeOH)
120		Light yellow liquid NMR (DMSO-d_6) δ ppm: 0.97 (3H, t, J=7.5Hz), 1.71 (2H, sex, J=7.5Hz), 3.66 (1H, dd, J=13.5, 5.5Hz), 3.70-3.80 (2H, m), 3.91 (2H, t, J=7.5Hz), 4.10 (1H, t, J=9Hz), 4.80-4.90 (1H, m), 6.95 (2H, d, J=9Hz), 7.43 (2H, d, J=9Hz) IR ν (liq.) cm^{-1}: 1756 MS (m/z): 276 (M^+) Optical Rotation $[\alpha]_D^{20}$-114.9° (c=0.1, DMSO)
121		Yellow liquid NMR (DMSO-d_6) δ ppm: 0.89 (3H, t, J=7.5Hz), 1.30 (2H, sex, J=7.5Hz), 1.54 (2H, quin, J=7.5Hz), 2.56 (2H, t, J=5Hz), 3.67 (1H, dd, J=13.5, 6Hz), 3.70-3.80 (2H, m), 4.13 (1H, t, J=9Hz), 4.80-4.90 (1H, m), 7.20 (2H, d, J=8.5Hz), 7.45 (2H, d, J=8.5Hz) IR ν (liq.) cm^{-1}: 1754, 2112 MS (m/z): 274 (M^+) Optical Rotation $[\alpha]_D^{20}$-132.6° (c=0.1, DMSO)
122		Colorless prisms [AcOEt-n-Hexane] mp, 90~91°C Elemental analysis $C_{16}H_{14}N_4O_3$ Theoretical C, 61.93; H, 4.55; N, 18.06 Experimental C, 62.10; H, 4.49; N, 17.97 Optical Rotation $[\alpha]_D^{20}$-140.4° (c=0.5, MeOH)



Reference example	R	Form and physical properties [Recrystallization solvent]
123		Light brown liquid NMR ($CDCl_3$) δ ppm: 3.61 (1H, dd, J=13, 4.5Hz), 3.75 (1H, dd, J=13, 4.5Hz), 3.87 (1H, dd, J=8.5, 6Hz), 4.10 (1H, t, J=8.5Hz), 4.75-4.85 (1H, m), 7.14 (1H, t, J=9Hz), 7.20-7.30 (3H, m), 7.63 (1H, dd, J=12.5, 3Hz), 8.35 (1H, d, J=3.5Hz), 8.38 (1H, d, J=2Hz) IR ν (liq.) cm^{-1}: 1756, 2112 MS (m/z): 329 (M^+) Optical Rotation $[\alpha]_D^{20}$-118.7° (c=0.1, DMSO)
124		Colorless platelets [EtOH] mp, 75~76°C Elemental analysis $C_{13}H_{15}FN_4O_4$ Theoretical C, 50.32; H, 4.87; N, 18.06 Experimental C, 50.27; H, 4.94; N, 18.01 Optical Rotation $[\alpha]_D^{20}$-119.8° (c=0.1, DMSO)
125		Colorless prisms [iso-Pr2O] mp, 91~92°C Elemental analysis $C_{14}H_{18}FN_5O_3$ Theoretical C, 52.01; H, 5.61; N, 21.66 Experimental C, 51.99; H, 5.44; N, 21.60 Optical Rotation $[\alpha]_D^{20}$-114.1° (c=0.1, DMSO)
126		Light yellow-brown liquid NMR (DMSO-d_6) δ ppm: 1.84 (2H, quin, J=6.5Hz), 2.14 (6H, s), 2.35 (2H, t, J=6.5Hz), 3.68 (1H, dd, J=13.5, 6Hz), 3.70-3.80 (2H, m), 4.06 (2H, t, J=6.5Hz), 4.11 (1H, t, J=9Hz), 4.80-4.90 (1H, m), 7.15-7.21 (2H, m), 7.53 (1H, dd, J=14, 2Hz) IR ν (liq.) cm^{-1}: 1754, 2112 MS (m/z): 337 (M^+) Optical Rotation $[\alpha]_D^{20}$-97.7° (c=0.1, DMSO)



Reference example	R	Form and physical properties [Recrystallization solvent]
127		Light brown liquid NMR (DMSO-d_6) δ ppm: 1.53 (2H, quin, J=7Hz), 1.72 (2H, quin, J=7Hz), 2.12 (6H, s), 2.24 (2H, t, J=7Hz), 3.67 (1H, dd, J=13.5, 5.5Hz), 3.73 (1H, dd, J=13.5, 3Hz), 3.75 (1H, dd, J=9, 6Hz), 4.04 (2H, t, J=7Hz), 4.11 (1H, t, J=9Hz), 4.83-4.89 (1H, m), 7.15-7.21 (2H, m), 7.52 (1H, dd, J=13.5, 2.5Hz) IR ν (liq.) cm^{-1}: 1754, 2112 MS (m/z): 351 (M^+) Optical Rotation $[\alpha]_D^{20}$-88.6° (c=0.1, DMSO)
128		Orange liquid NMR ($CDCl_3$) δ ppm: 2.25 (6H, s), 2.48 (2H, t, J=7.5Hz), 2.85 (3H, s), 3.23 (2H, t, J=7.5Hz), 3.59 (1H, dd, J=13.5, 4.5Hz), 3.69 (1H, dd, J=13.5, 4.5Hz), 3.81 (1H, dd, J=9, 6Hz), 4.04 (1H, t, J=9Hz), 4.70-4.80 (1H, m), 6.91 (1H, t, J=9Hz), 7.10 (1H, dd, J=9, 2.5Hz), 7.37 (1H, dd, J=14.5, 2.5Hz) IR ν (liq.) cm^{-1}: 1754, 2112 MS (m/z): 336 (M^+) Optical Rotation $[\alpha]_D^{20}$-112.6° (c=0.1, DMSO)
129		Colorless needles [iso-PrOH] mp, 104~105.5°C Elemental analysis $C_{14}H_{16}N_4O_2$ Theoretical C, 61.75; H, 5.92; N, 20.58 Experimental C, 61.64; H, 5.73; N, 20.54 Optical Rotation $[\alpha]_D^{20}$-135.9° (c=0.1, DMSO)

Reference Example 130: (R)-5-Azidomethyl-3-[3-fluoro-4-(piperazin-1-yl)phenyl]-2-oxooxazolidine

20 mL of a 16% hydrogen chloride ethyl acetate solution containing 1.0 g of (R)-5-azidomethyl-3-[(4-tert-butoxycarbonylpiperazin-1-yl)-3-fluorophenyl]-2-oxooxazolidine was stirred for 30 minutes at room temperature, and the precipitated crystals were collected by filtration. A 10% sodium hydroxide aqueous solution and water were added to the crystals to render it alkaline, and extraction was performed with ethyl acetate. The extract was washed with saturated sodium chloride aqueous solution, and after drying with anhydrous sodium sulfate, the solvent was evaporated off under reduced pressure to obtain 0.72 g of light brown crystals. The crystals were recrystallized from isopropanol to obtain colorless crystals with a melting point of 114-115°C.

Elemental analysis $C_{14}H_{17}FN_6O_2$

Theoretical values: C 52.49; H 5.35; N 26.24

Experimental values: C 52.24; H 5.21; N 26.15

Optical Rotation $[\alpha]_D^{20}$: -127.3° (c=0.1, DMSO)

Reference Example 131: Ethyl (R)-3-[4-[4-(5-azidomethyl-2-oxooxazolidine-3-yl)-2-fluorophenyl]piperazin-1-yl]propionate

70 mL of an ethanol solution containing 7.00 g of (R)-5-azidomethyl-3-[3-fluoro-4-(piperazin-1-yl)phenyl]-2-oxooxazolidine and 3.56 mL of ethyl acrylate was heated at reflux for 1 h. The solvent was evaporated off under reduced pressure and the material was purified cy column chromatography (silica gel, diethyl ether) to obtain 7.50 g of colorless crystals. The crystals ere recrystallized form isopropanol to obtain colorless crystals with a melting point of 82-83°C.

Elemental analysis $C_{19}H_{25}FN_6O_4$

Theoretical: C 54.28; H 5.99; N 19.99

Experimental: C 53.99; H 5.88; N 19.97

Optical Rotation $[\alpha]_D^{20}$: -95.0° (c=0.1, DMSO)

Reference Example 132: (R)-5-Azidomethyl-3-[4-(4-n-butylpiperazin-1-yl)-3-fluorophenyl]-2-oxooxazoline

10 mL of an N,N-dimethylformamide solution containing 2.00 g of (R)-5-azidomethyl-3-[3-fluoro-4-(piperazin-1-yl)phenyl]-2-oxooxazolidine, 0.74 mL of n-butyl bromide and 0.86 g of potassium carbonate was stirred for 3 hours at 60°C. Water was added to the reaction solution, and the precipitated crystals were filtered to obtain 1.93 g of light yellow crystals. The crystals were recrystallized from isopropanol to obtain light yellow scales with a melting point of 102-103°C.

Elemental analysis $C_{18}H_{25}FN_6O_2 \cdot 1/8H_2O$

Theoretical: C 57.09; H 6.72; N 22.19

Experimental: C 57.10; H 6.86; N 22.20

Optical Rotation $[\alpha]_D^{20}$: -104.8° (c=0.1, DMSO)

Reference Example 133: (R)-5-Azidomethyl-3-[3-fluoro-4-[4-(3-methoxypropionyl)piperazin-1-yl]phenyl]-2-oxooxazolidine

10 mL of a tetrahydrofuran solution containing 2.30 g of 3-methoxypropionyl chloride was added dropwise to 50 mL of a tetrahydrofuran solution containing 5.00 g of (R)-5-azidomethyl-3-[3-fluoro-4-(piperazin-1-yl)phenyl]-2-oxooxazolidine and 3.26 mL of triethylamine while stirring and chilling on ice, and the solution was stirred for 1 hour while chilling on ice. Water was added to the reaction solution, and the solution was extracted with ethyl acetate. The extract was then washed in sequence with dilute hydrochloric acid, saturated sodium hydrogen carbonate aqueous solution and saturated sodium chloride aqueous solution, and after drying on anhydrous sodium sulfate, the solvent was evaporated off under reduced pressure. The residue was crystallized in a mixed solution of isopropanol diisopropyl ether, and the crystals that were collected by filtration were washed with diisopropyl ether to obtain 4.35 g of light yellow crystals. The crystals were recrystallized from ethanol to obtain light yellow prisms with a melting point of 99-101°C.

Elemental analysis $C_{18}H_{23}FN_6O_4$

Theoretical: C 53.20; H 5.70; N 20.68

Experimental C 53.07; H 5.68; N 20.75

Optical Rotation $[\alpha]_D^{20}$: -106.9° (c=0.1, DMSO)

The compound of Reference Example 134 was obtained in the same manner as in Reference Example 133.

Reference Example 134: (R)-5-Azidomethyl-3-[4-(benzyloxyacetylpiperazin-1-yl)-3-fluorophenyl]-2-oxooxazolidine

Form: Colorless needles (recrystallization solvent: EtOH)

Melting point: 101-102°C

Elemental analysis $C_{23}H_{25}FN_6O_4$

Theoretical: C 58.97; H 5.38; N 17.94

Experimental: C 58.88; H 5.32; N 17.95

Optical Rotation $[\alpha]_D^{20}$: -89.6° (c=0.1, DMSO)

Reference Example 135 (S)-5-Aminomethyl-2-oxo-3-[4-(thiomorpholin-4-yl)phenyl]oxazolidine

130 mL of a colorless tetrahydrofuran solution containing 8.50 g of (R)-5-azidomethyl-2-oxo-3-[4-(thiomorpholin-4-yl)phenyl]oxazolidine and 7.68 g of triphenylphosphine was stirred for 15 h at room temperature. 4.8 mL of water was added to this mixed solution, and the solution was stirred for 14 hours at 40°C. After chilling, water was added to the reaction solution and the solution was rendered acidic with 10% hydrochloric acid before washing with diethyl ether. The aqueous layer was rendered alkaline with potassium carbonate, and was extracted with a dichloromethane-methanol mixed solution. The extract was washed with saturated sodium chloride aqueous solution, and after drying on anhydrous sodium sulfate, the solvent was evaporated off under reduced pressure to obtain 6.88 g of colorless crystals. The crystals were recrystallized from ethyl acetate to obtain colorless crystals with a melting point of 119.5-121°C.

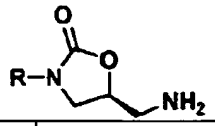
Elemental analysis $C_{14}H_{19}N_3O_2S$

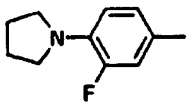
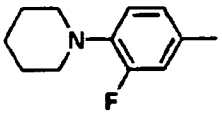
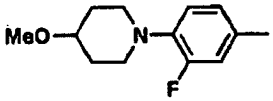
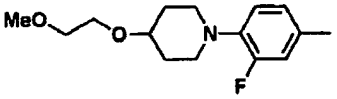
Theoretical: C 57.31; H 6.53; N 14.32

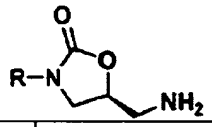
Experimental: C 57.36; H 6.45; N 14.06

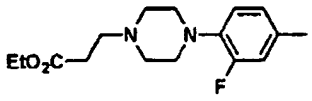
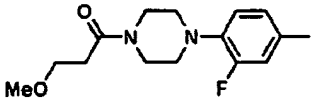
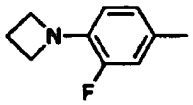
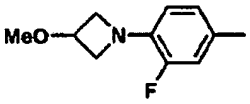
Optical Rotation $[\alpha]_D^{20}$: -35.9° (c=0.1, DMSO)

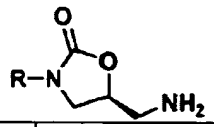
The compounds of Reference Examples 136-163 were obtained in the same manner as in Reference Example 135.

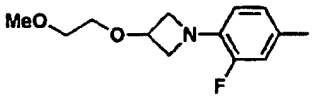
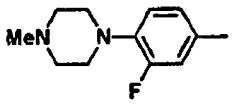
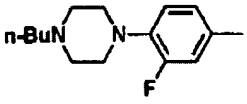


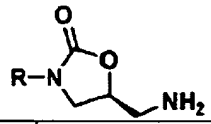
Reference example	R	Form and physical properties [Recrystallization solvent]
136		Colorless crystals [AcOEt] mp, 100~101.5°C Elemental analysis $C_{14}H_{18}FN_3O_2$ Theoretical C, 60.20; H, 6.50; N, 15.04 Experimental C, 60.16; H, 6.44; N, 15.18 Optical Rotation $[\alpha]_D^{20}$-38.9° (c=0.1, DMSO)
137		Light brown crystals [iso-PrOH-iso-Pr_2O] mp, 90~92°C Elemental analysis $C_{15}H_{20}FN_3O_2$ Theoretical C, 61.42; H, 6.87; N, 14.32 Experimental C, 61.16; H, 6.56; N, 14.40 Optical Rotation $[\alpha]_D^{20}$-36.1° (c=0.1, DMSO)
138		Colorless needles [AcOEt-iso-Pr_2O] mp, 102~102.5°C Elemental analysis $C_{16}H_{22}FN_3O_3$ Theoretical C, 59.43; H, 6.86; N, 12.99 Experimental C, 59.13; H, 6.72; N, 12.89 Optical Rotation $[\alpha]_D^{20}$-35.0° (c=0.1, DMSO)
139		Light brown crystals NMR (DMSO-d_6) δ ppm: 1.52 (2H, brs), 1.55-1.65 (2H, m), 1.90-2.00 (2H, m), 2.70-2.85 (3H, m), 2.85 (1H, dd, J=13.5, 5Hz), 3.15-3.25 (2H, m), 3.27 (3H, s), 3.40-3.50 (1H, m), 3.45 (2H, t, J=5Hz), 3.56 (2H, t, J=5Hz), 3.81 (1H, dd, J=9, 6.5Hz), 4.01 (1H, t, J=9Hz), 4.55-4.65 (1H, m), 7.05 (1H, t, J=9Hz), 7.17 (1H, dd, J=9, 2.5Hz), 7.46 (1H, dd, J=15, 2.5Hz) IR ν (liq.) cm^{-1}: 1744, 3380 MS (m/z): 367 (M^+) Optical Rotation $[\alpha]_D^{20}$-30.1° (c=0.1, DMSO)

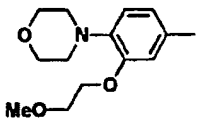
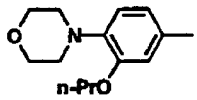
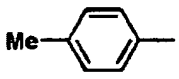


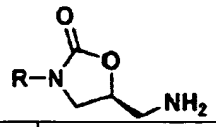
Reference example	R	Form and physical properties [Recrystallization solvent]
140		Colorless crystals [iso-PrOH-iso-Pr_2O] mp, 88~88.5°C Elemental analysis $C_{19}H_{27}FN_4O_4$ Theoretical C, 57.85; H, 6.90; N, 14.20 Experimental C, 57.57; H, 7.15; N, 14.06 Optical Rotation $[\alpha]_D^{20}$-30.0° (c=0.1, DMSO)
141		Light yellow crystals [iso-PrOH] mp, 134~135°C Elemental analysis $C_{18}H_{25}FN_4O_4$ Theoretical C, 56.83; H, 6.62; N, 14.73 Experimental C, 56.86; H, 6.74; N, 14.66 Optical Rotation $[\alpha]_D^{20}$-35.0° (c=0.1, DMSO)
142		Grey-white needles NMR (DMSO-d_6) δ ppm: 1.58 (2H, brs), 2.27 (2H, quin, J=7.5Hz), 2.80 (1H, dd, J=13.5, 5Hz), 2.83 (1H, dd, J=13.5, 5Hz), 3.78 (1H, dd, J=8.5, 6.5Hz), 3.85 (4H, td, J=7.5, 2Hz), 3.98 (1H, t, J=8.5Hz), 4.50-4.60 (1H, m), 6.53 (1H, dd, J=10.5, 8.5Hz), 7.11 (1H, dd, J=8.5, 2.5Hz), 7.36 (1H, dd, J=14.5, 2.5Hz) IR ν (KBr) cm^{-1}: 1722, 3408 MS (m/z): 265 (M^+) Optical Rotation $[\alpha]_D^{20}$-40.1° (c=0.1, DMSO)
143		Light brown crystals [AcOEt] mp, 105~106.5°C Elemental analysis $C_{14}H_{18}FN_3O_3$ Theoretical C, 56.94; H, 6.14; N, 14.23 Experimental C, 56.68; H, 5.92; N, 14.00 Optical Rotation $[\alpha]_D^{20}$-36.1° (c=0.1, DMSO)

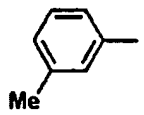
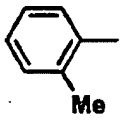
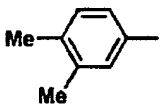


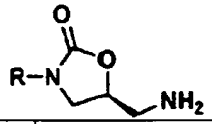
Reference example	R	Form and physical properties [Recrystallization solvent]
144		Brown liquid NMR (DMSO-d_6) δ ppm: 1.54 (2H, brs), 2.79 (1H, dd, J=13.5, 5Hz), 2.84 (1H, dd, J=13.5, 5Hz), 3.26 (3H, s), 3.45 (2H, t, J=4.5Hz), 3.53 (2H, t, J=4.5Hz), 3.60-3.65 (2H, m), 3.78 (1H, dd, J=8.5, 6.5Hz), 3.98 (1H, t, J=8.5Hz), 4.05-4.15 (2H, m), 4.35-4.45 (1H, m), 4.50-4.60 (1H, m), 6.57 (1H, t, J=8.5Hz), 7.12 (1H, dd, J=8.5, 2Hz), 7.38 (1H, dd, J=14.5, 2Hz) IR ν (liq.) cm^{-1}: 1744, 3384 MS (m/z): 339 (M^+) Optical Rotation $[\alpha]_D^{20}$-27.9° (c=0.1, DMSO)
145		Light yellow crystals NMR (DMSO-d_6) δ ppm: 1.89 (2H, brs), 2.22 (3H, s), 2.46 (4H, t, J=5Hz), 2.79 (1H, dd, J=14, 5Hz), 2.84 (1H, dd, J=14, 5Hz), 2.98 (4H, t, J=5Hz), 3.81 (1H, dd, J=9, 6Hz), 4.01 (1H, t, J=9Hz), 4.54-4.61 (1H, m), 7.03 (1H, t, J=8.5Hz), 7.18 (1H, dd, J=8.5, 2Hz), 7.46 (1H, dd, J=15.5, 2Hz) IR ν (KBr) cm^{-1}: 1734, 3328, 3372 MS (m/z): 308 (M^+) Optical Rotation $[\alpha]_D^{20}$-34.0° (c=0.1, DMSO)
146		Light yellow crystals [iso-PrOH-iso-Pr_2O] mp, 98~100°C Elemental analysis $C_{18}H_{27}FN_4O_2 \cdot 2/5H_2O$ Theoretical C, 60.45; H, 7.83; N, 15.67 Experimental C, 60.62; H, 7.81; N, 15.46 Optical Rotation $[\alpha]_D^{20}$-34.1° (c=0.1, DMSO)

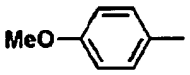
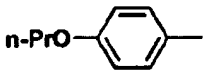
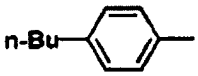
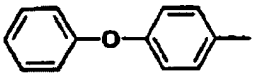


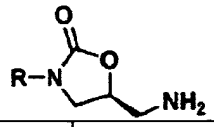
Reference example	R	Form and physical properties [Recrystallization solvent]
147		Colorless crystals NMR (DMSO-d_6) δ ppm: 1.51 (2H, brs), 2.80 (1H, dd, J=13.5, 5Hz), 2.85 (1H, dd, J=13.5, 5Hz). 2.96 (4H, t, J=5Hz), 3.33 (3H, s), 3.68 (2H, t, J=5Hz), 3.71 (4H, t, J=5Hz), 3.81 (1H, dd, J=9, 6.5Hz), 4.02 (1H, t, J=9Hz), 4.09 (2H, t, J=5Hz), 4.52-4.60 (1H, m), 6.87 (1H, d, J=8.5Hz), 6.98 (1H, dd, J=8.5, 2.5Hz), 7.27 (1H, d, J=2.5Hz) IR ν (liq.) cm^{-1}: 1748, 3496 MS (m/z): 351 (M^+) Optical Rotation $[\alpha]_D^{20}$-25.0° (c=0.1, DMSO)
148		Light brown crystals NMR (DMSO-d_6) δ ppm: 1.01 (3H, t, J=7.5Hz), 1.58 (2H, brs), 1.76 (2H, sex, J=7.5Hz), 2.75-2.90 (2H, m), 2.95 (4H, t, J=5Hz), 3.72 (4H, t, J=5Hz), 3.81 (1H, dd, J=9, 6.5Hz), 3.93 (2H, t, J=7.5Hz), 4.02 (1H, t, J=9Hz), 4.53-4.60 (1H, m), 6.87 (1H, d, J=9Hz), 6.94 (1H, dd, J=9, 2.5Hz), 7.29 (1H, d, J=2.5Hz) IR ν (KBr) cm^{-1}: 1732, 3388 MS (m/z): 335 (M^+) Optical Rotation $[\alpha]_D^{20}$-28.0° (c=0.1, DMSO)
149		Colorless amorphous solid NMR (DMSO-d_6) δ ppm: 2.27 (3H, s), 2.80 (1H, dd, J=13.5, 5Hz), 2.85 (1H, dd, J=13.5, 5Hz), 3.07 (2H, brs), 3.82 (1H, dd, J=8.5, 6Hz), 4.02 (1H, t, J=8.5Hz), 4.53-4.61 (1H, m), 7.18 (2H, d, J=8.5Hz), 7.43 (2H, d, J=8.5Hz) IR ν (KBr) cm^{-1}: 1748, 3356 MS (m/z): 206 (M^+) Optical Rotation $[\alpha]_D^{20}$-38.1° (c=0.1, DMSO)

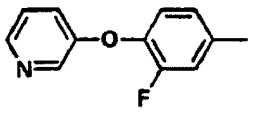
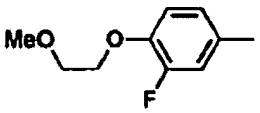
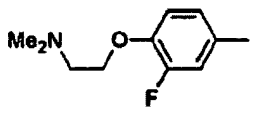


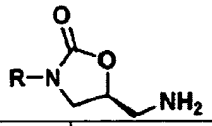
Reference example	R	Form and physical properties [Recrystallization solvent]
150		Colorless liquid NMR (DMSO-d_6) δ ppm: 1.52 (2H, brs), 2.31 (3H, s), 2.80 (1H, dd, J=13.5, 5.5Hz), 2.86 (1H, dd, J=13.5, 5.5Hz), 3.83 (1H, dd, J=8.5, 6Hz), 4.04 (1H, t, J=8.5Hz), 4.55-4.61 (1H, m), 6.93 (1H, d, J=8Hz), 7.25 (1H, t, J=8Hz), 7.35-7.40 (2H, m) IR ν (liq.) cm^{-1}: 1748, 3392 MS (m/z): 206 (M^+) Optical Rotation $[\alpha]_D^{20}$-36.9° (c=0.1, DMSO)
151		Light yellow liquid NMR ($CDCl_3$) δ ppm: 1.43 (2H, brs), 2.31 (3H, s), 3.00 (1H, dd, J=13.5, 6Hz), 3.11 (1H, dd, J=13.5, 3.5Hz), 3.74 (1H, dd, J=8.5, 6Hz), 3.94 (1H, t, J=8.5Hz), 4.70-4.80 (1H, m), 7.20-7.30 (4H, m) IR ν (liq.) cm^{-1}: 1748, 3392 MS (m/z): 206 (M^+) Optical Rotation $[\alpha]_D^{20}$-48.5° (c=0.5, MeOH)
152		Light yellow crystals NMR (DMSO-d_6) δ ppm: 1.60 (2H, brs), 2.19 (3H, s), 2.22 (3H, s), 2.80 (1H, dd, J=13.5, 5.5Hz), 2.85 (1H, dd, J=13.5, 5.5Hz), 3.81 (1H, dd, J=9, 6Hz), 4.01 (1H, t, J=9Hz), 4.50-4.60 (1H, m), 7.11 (1H, d, J=8.5Hz), 7.27 (1H, dd, J=8.5, 2.5Hz), 7.32 (1H, d, J=2.5Hz) IR ν (KBr) cm^{-1}: 1730, 3420 MS (m/z): 220 (M^+) Optical Rotation $[\alpha]_D^{20}$-37.0° (c=0.1, DMSO)

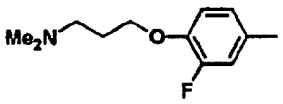
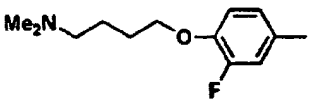
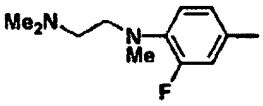
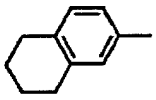


Reference example	R	Form and physical properties [Recrystallization solvent]
153		Colorless prisms [AcOEt–n–Hexane] mp, 80~81°C Elemental analysis $C_{11}H_{14}N_2O_3$ Theoretical C, 59.45; H, 6.35; N, 12.61 Experimental C, 59.49; H, 6.32; N, 12.60 Optical Rotation $[\alpha]_D^{20}$–59.0° (c=0.5, MeOH)
154		Colorless crystals NMR (DMSO-d_6) δ ppm: 0.97 (3H, t, J=7.5 Hz), 1.71 (2H, sex, J=7.5Hz), 2.80 (1H, dd, J= 13.5, 5Hz), 2.85 (1H, dd, J=13.5, 5Hz), 3.10 (2H, brs), 3.81 (1H, dd, J=8.5, 6.5 Hz), 3.91 (2H, t, J=7.5 Hz), 4.01 (1H, t, J= 8.5 Hz), 4.50-4.60 (1H, m), 6.94 (2H, d, J=9Hz), 7.44 (2H, d, J=9Hz) IR ν (KBr) cm^{-1}: 1732, 3336 Optical Rotation $[\alpha]_D^{20}$–37.0° (c= 0.1, DMSO)
155		Colorless crystals NMR (DMSO-d_6) δ ppm: 0.89 (3H, t, J=7.5 Hz), 1.30 (2H, sex, J=7.5Hz), 1.54 (2H, quin, J=7.5 Hz), 2.55 (2H, t, J=7.5 Hz), 2.80, (1H, dd, J=13.5, 5Hz), 2.85 (1H, dd, J=13.5, 5Hz) 3.13 (2H, brs) 3.83 (1H, dd, J=9, 6.5Hz), 4.03 (1H, t, J=9Hz), 7.18 (2H, d, J= 8.5Hz), 7.45 (2H, d, J=8.5Hz) IR ν (KBr) cm^{-1}: 1748, 3356 MS (m/z): 248 (M^+) Optical Rotation $[\alpha]_D^{20}$–35.8° (c =0.1, DMSO)
156		Colorless prisms (AcOEt] mp, 110~111°C Elemental analysis $C_{16}H_{16}N_2O_3$ Theoretical C, 67.59; H, 5.67; N, 9.85 Experimental C, 67.31; H, 5.69; N, 9.84 Optical Rotation $[\alpha]_D^{20}$–51.5 ° (c=0.5, MeOH)



Reference example	R	Form and physical properties [Recrystallization solvent]
157		Light yellow crystals [AcOEt-n-Hexane] mp, 78~79°C Elemental analysis $C_{15}H_{14}FN_3O_3$ Theoretical C, 59.40; H, 4.65; N, 13.85 Experimental C, 59.35; H, 4.73; N, 13.77 Optical Rotation $[\alpha]_D^{20}$ –40.1° (c=0.1, DMSO)
158		Light yellow crystals NMR ($CDCl_3$) δ ppm: 1.31 (2H, brs), 2.98 (1H, dd, J=13.5, 4.5Hz), 3.11 (1H, dd, J=13.5, 4.5Hz), 3.45 (3H, s), 3.76 (2H, t, J=4.5Hz), 3.82 (1H, dd, J=8.5, 6.5Hz), 4.00 (1H, t, J=8.5Hz), 4.18 (2H, t, J= 4.5 Hz), 4.60-4.70 (1H, m), 7.00 (1H, t, J= 9Hz), 7.10-7.20 (1H, m), 7.47 (1H, dd, J=13, 3Hz) IR ν (KBr) cm^{-1}: 1746, 3328, 3396 MS (m/z): 284 (M^+) Optical Rotation $[\alpha]_D^{20}$ –33.0° (c=0.1, DMSO)
159		Colorless crystals NMR (DMSO-d_6) δ ppm: 2.22 (6H, s), 2.63 (2H, t, J=6Hz), 2.80 (1H, dd, J=13.5, 5Hz), 2.86 (1H, dd, J=13.5, 5Hz), 3.19 (2H, brs), 3.82 (1H, dd, J=8.5, 6.5Hz), 4.02 (1H, t, J=8.5Hz), 4.10 (2H, t, J=6Hz), 4.55-4.61 (1H, m), 7.14-7.21 (2H, m), 7.52 (1H, dd, J=15.5, 2.5Hz) IR ν (KBr) cm^{-1}: 1730, 3328 MS (m/z): 297 (M^+) Optical Rotation $[\alpha]_D^{20}$ –40.0° (c=0.1, DMSO)



Reference example	R	Form and physical properties [Recrystallization solvent]
160		Light yellow prisms [iso-PrOH-iso-Pr_2O] mp, 61~63 °C Elemental analysis $C_{15}H_{22}FN_3O_3$ Theoretical C, 57.86; H, 7.12; N, 13.50 Experimental C, 57.61; H, 6.78; N, 13.19 Optical Rotation $[\alpha]_D^{20}$–33.1° (c=0.1, DMSO)
161		Colorless amorphous solid NMR (DMSO-d_6) δ ppm: 1.53 (2H, quin, J=7Hz), 1.55 (2H, brs), 1.72 (2H, quin, J=7Hz), 2.12 (6H, s), 2.24 (2H, t, J=7Hz), 2.79 (1H, dd, J=13.5, 5Hz), 2.85 (1H, dd, J=13.5, 5Hz), 3.82 (1H, dd, J=9, 6Hz), 4.02 (1H, t, J=9Hz), 4.03 (2H, t, J=7Hz), 4.54-4.61 (1H, m), 7.16 (1H, t, J-9Hz), 7.19 (1H, dd, J=9, 2.5Hz), 7.54 (1H, dd, J=14, 2.5Hz) IR ν (KBr) cm^{-1}: 1728, 3336, 3420 MS (m/z): 325 (M^+) Optical Rotation $[\alpha]_D^{20}$-24.1° (c=0.1, DMSO)
162		Light brown liquid NMR ($CDCl_3$) δ ppm: 1.44 (2H, brs), 2.26 (6H, s), 2.48 (2H, t, J=7.5Hz), 2.84 (3H, s), 2.97 (1H, dd, J=13.5, 5Hz), 3.10 (1H, dd, J=13.5, 5Hz), 3.22 (2H, t, J=7.5Hz), 3.81 (1H, dd, J=8.5, 6.5Hz), 4.00 (1H, t, J=8.5Hz), 4.60-4.70 (1H, m), 6.91 (1H, t, J=9Hz), 7.05-7.15 (1H, m), 7.38 (1H, dd, J=14.5, 2.5Hz) IR ν (liq.) cm^{-1}: 1750, 3384 MS (m/z): 310 (M^+) Optical Rotation $[\alpha]_D^{20}$-34.8° (c=0.1, DMSO)
163		Colorless prisms [iso-PrOH-n-Hexane] mp, 81~82.5 °C Elemental analysis $C_{14}H_{18}N_2O_2$ Theoretical C, 68.27; H, 7.37; N, 11.37 Experimental C, 68.03; H, 7.53: N, 11.31 Optical Rotation $[\alpha]_D^{20}$-36.0° (c=0.1, DMSO)

Reference Example 164: (S)-5-Aminomethyl-3-[3-fluoro-4-[4-(hydroxyacetyl)piperazin-1-yl]phenyl]-2-oxooxazolidine

300 mL of a methanol dispersion containing 5.10 g of (R)-5-azidomethyl-3-[4-[4-(benzyloxyacetyl)piperazin-1-yl]-3-fluorophenyl]-2-oxooxazolidine and 1.00 g of 5% palladium carbon and 5.00 mL of a 40% hydrogen chloride methanol solution was stirred for 12 hours at 60°C and a hydrogen pressure of 70 kg/cm^2. After the reaction, the catalyst was filtered out and the solvent was evaporated off under reduced pressure. Water and 10% sodium hydride aqueous solution was added to the residue to render the solution alkaline, and the solution was then extracted with a 1,2-dichloromethane-methanol mixed solution. The extract was dried on anhydrous sodium sulfate and the solvent was evaporated of under reduced pressure. Isopropanol was added to the residue and the precipitated crystals were removed by filtration and washed with diisopropyl ether to obtain 2.63 g of colorless crystals.

IR spectrum ν (liq.) cm^{-1}: 1754, 3432

NMR spectrum (DMSO-d_6) δ ppm:

2.95-3.00 (4H, m), 3.10-3.30 (2H, m), 3.40-3.70 (4H, m), 3.87 (1H, dd, J=9, 6.5 Hz), 4.12 (2H, s), 4.15 (1H, t, J=9 Hz), 4.52 (1H, brs), 4.85-4.95 (1H, m), 7.08 (1H, t, J=9 Hz), 7.19 (1H, dd, J=9, 2.5 Hz), 7.48 (1H, dd, J=14.5, 2.5 Hz), 8.12 (2H, brs)

Mass spectrum m/z: 352 (M^+)

Optical Rotation $[\alpha]_D^{20}$: -38.2° (c=0.1, DMSO)

Reference Example 165: (R)-N-[2-Oxo-3-[4-(thiomorpholin-4-yl)phenyl]oxazolidin-5-yl]methylisothiocyanate

0.5 mL of triethylamine and 0.2 mL of carbon disulfide were added to a mixed solution of 1 mL of N,N-dimethylformamide and 10 mL of benzene containing 1.00 g of (S)-5-aminomethyl-2-oxo-3-[4-(thiomorpholin-4-yl)phenyl]oxazolidine, and the solution was stirred for 6 hours at room temperature. The reaction solution was then concentrated under reduced pressure, and 10 mL of dichloromethane and 0.5 mL of triethylamine were added to the residue. 0.35 mL of ethyl chlorocarbonate was then added to the mixed solution while stirring and chilling on ice, and the solution was stirred for 30 minutes at the same temperature. Water was added to the reaction solution, and the precipitated

crystals were filtered to obtain 0.98 g of colorless crystals. The crystals were recrystallized from a mixed solution of N,N-dimethylformamide and water to obtain colorless crystals with a melting point of 194.5-195.5°C.

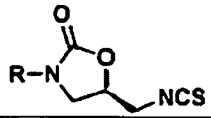
Elemental analysis $C_{15}H_{17}N_3O_2S_2$

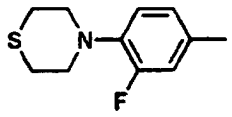
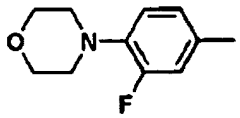
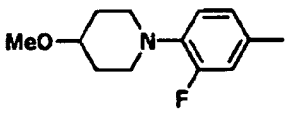
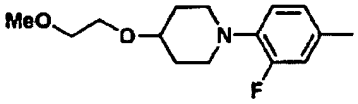
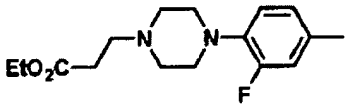
Theoretical: C 53.71; H 5.11; N 12.53

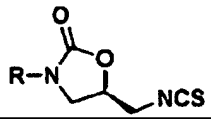
Experimental: C 53.53; H 5.07; N 12.54

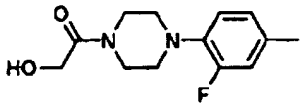
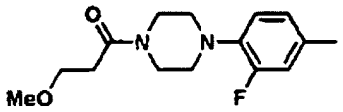
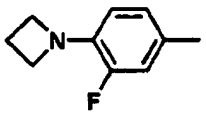
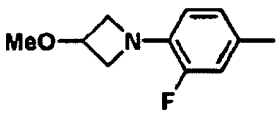
Optical Rotation $[\alpha]_D^{20}$: -151.8° (c=0.1, DMSO)

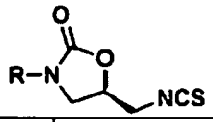
The compounds of Reference Examples 166-194 were obtained in the same manner as in Reference Example 165.

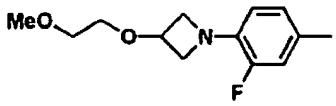
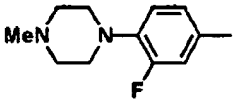
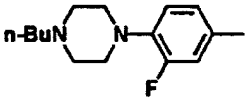
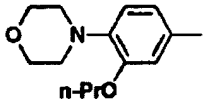


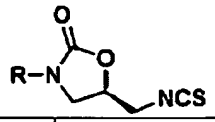
Reference example	R	Form and physical properties [Recrystallization solvent]
166		Light yellow cylinders [CH_3CN] mp, 135.5~136.5°C Elemental analysis $C_{15}H_{16}FN_3O_2S_2$ Theoretical C, 50.97; H, 4.56; N, 11.89 Experimental C, 51.01; H, 4.60; N, 11.85 Optical Rotation $[\alpha]_D^{20}$-151.9° (c=0.1, DMSO)
167		Brown liquid NMR ($CDCl_3$) δ ppm: 3.06 (4H, t, J=5Hz), 3.83-3.86 (2H, m), 3.87 (4H, t, J=5Hz), 3.96 (1H, dd, J=15, 5.5Hz), 4.15 (1H, t, J=9Hz), 4.79-4.85 (1H, m), 6.95 (1H, t, J=9Hz), 7.13 (1H, dd, J=9, 2Hz), 7.43 (1H, dd, J=14.5, 2Hz) IR (liq.): 1754, 2096 MS (m/z): 337 (M^+) $[\alpha]_D^{20}$-139.1° (c=0.08, DMSO)
168		Colorless prisms [AcOEt-iso-Pr_2O] mp, 118.5~120°C Elemental analysis $C_{17}H_{20}FN_3O_3S$ Theoretical C, 55.88; H, 5.52; N, 11.50 Experimental C, 55.89; H, 5.58; N, 11.41 Optical Rotation $[\alpha]_D^{20}$-146.6° (c=0.1, DMSO)
169		Colorless crystals[AcOEt-iso-Pr_2O] mp, 63~64°C Elemental analysis $C_{19}H_{24}FN_3O_4S$ Theoretical C, 55.73; H, 5.91; N, 10.26 Experimental C, 55.64; H, 5.99; N, 10.27 Optical Rotation $[\alpha]_D^{20}$-130.7°C (c=0.1, DMSO)
170		Light yellow needles [iso-PrOH] mp, 92.5~94°C Elemental analysis $C_{20}H_{25}FN_4O_4S$ Theoretical C, 55.03; H, 5.77; N, 12.84 Experimental C, 54.84; H, 5.87; N, 12.71 Optical Rotation $[\alpha]_D^{20}$-121.8° (c=0.1, DMSO)

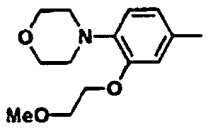
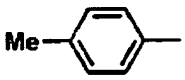
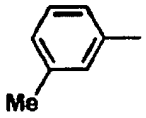
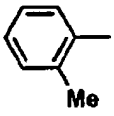


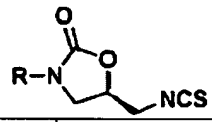
Reference example	R	Form and physical properties [Recrystallization solvent]
171		Light brown needles [EtOH] mp, 139~141°C Elemental analysis $C_{17}H_{19}FN_4O_4S$ Theoretical C, 51.77; H, 4.86; N, 14.20 Experimental C, 51.48; H, 5.03; N, 14.03 Optical Rotation $[\alpha]_D^{20}$-130.5°C (c=0.1, DMSO)
172		Light yellow crystals [MeOH] mp, 110~112°C Elemental analysis $C_{19}H_{23}FN_4O_4S \cdot 1/4H_20$ Theoretical C, 53.45; H, 5.55; N, 13.12 Experimental C, 53.60; H, 5.46; N, 13.04 Optical Rotation $[\alpha]_D^{20}$-123.9°C (c=0.1, DMSO)
173		Light brown liquid NMR (DMSO-d_6) δ ppm: 2.28 (2H, quin, J=7.5 Hz), 3.74 (2H, dd, J=9, 5.5 Hz), 3.87 (4H, td, J=7.5, 2Hz), 4.00 (1H, dd, J=15, 5Hz), 4.10 (1H, dd, J=15, 3.5 Hz), 4.14 (1H, t, J=9Hz), 4.85-4.95 (1H, m), 6.54 (1H, dd, J=10, 9Hz), 7.11 (1H, dd, J=9, 2.5 Hz), 7.34 (1H, dd, J=14.5, 2.5Hz) IR ν (liq.) cm^{-1}: 1754, 2092 MS (m/z): 307 (M^+) Optical Rotation $[\alpha]_D^{20}$-155.8° (c=0.1, DMSO)
174		Brown liquid NMR (DMSO-d_6) δ ppm: 3.24 (3H, s), 3.60-3.70 (2H, m), 3.75 (1H, dd, J=9, 5.5 Hz), 3.95-4.20 (5H, m), 4.25-4.35 (1H, m), 4.85-4.95 (1H, m), 6.59 (1H, dd, J=10.5, 8.5Hz), 7.12 (1H, dd, J=8.5, 2.5Hz), 7.36 (1H, dd, J=14.5, 2.5Hz) IR ν (liq.) cm^{-1}: 1754, 2100 MS (m/z): 337 (M^+) Optical Rotation $[\alpha]_D^{20}$-129.3° (c=0.1, DMSO)

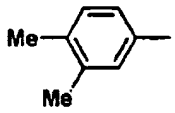
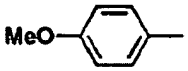
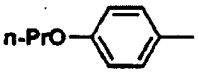
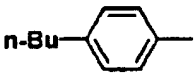


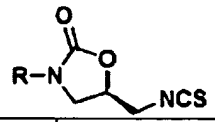
Reference example	R	Form and physical properties [Recrystallization solvent]
175		Colorless needles [Ac0Et-iso-$Pr_2$0] Mp, 78.5~79.5°C Elemental analysis $C_{17}H_{20}FN_3O_4S$ Theoretical C, 53.53; H, 5.29; N, 11.02 Experimental C, 53.47; H, 5.47; N, 10.93 Optical Rotation $[\alpha]_D^{20}$-140.4° (c=0.1, DMSO)
176		Colorless prisms [THF-iso-Pr_2O] mp, 127~127.5°C Elemental analysis $C_{16}H_{19}FN_4O_2S$ Theoretical C, 54.84; H, 5.47; N, 15.99 Experimental C, 54.83; H, 5.41; N, 15.84 Optical Rotation $[\alpha]_D^{20}$-159.0° (c=0.1, DMSO)
177		Light yellow platelets [iso-PrOH] mp, 101~102°C Elemental analysis $C_{19}H_{25}FN_4O_2S$ Theoretical C, 58.14; H, 6.42; N, 14.27 Experimental C, 58.06; H, 6.51; N, 14.16 Optical Rotation $[\alpha]_D^{20}$-133.8° (c=0.1, DMSO)
178		Colorless liquid NMR (DMSO-d_6) δ ppm: 1.01 (3H, t, J=7.5Hz), 1.76 (2H, sex, J=7.5Hz), 2.96 (4H, t, J=5Hz), 3.72 (4H, t, J=5Hz), 3.78 (1H, dd, J=9, 5.5Hz), 3.93 (2H, t, J=7.5Hz), 4.02 (1H, dd, J=15.5, 5Hz), 4.11 (1H, dd, J=15.5, 3.5Hz), 4.18 (1H, t, J=9Hz), 4.88-4.96 (1H, m), 6.88 (1H, d, J=9Hz), 6.94 (1H, dd, J=9, 2.5Hz), 7.25 (1H, d, J=2.5Hz) IR ν (liq.) cm^{-1}: 1756, 2092 MS (m/z): 377 (M^+) Optical Rotation $[\alpha]_D^{20}$-137.1° (c=0.1, DMSO)

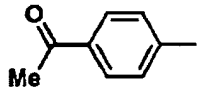
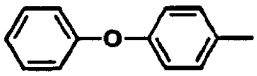
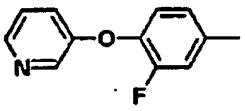
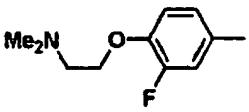


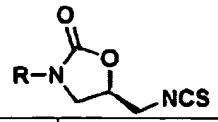
Reference example	R	Form and physical properties [Recrystallization solvent]
179		Light yellow liquid NMR (DMSO-d_6) δ ppm: 2.97 (4H, t, J=5Hz), 3.33 (3H, s), 3.68 (2H, t, J=5Hz), 3.72 (4H, t, J=5Hz), 3.78 (1H, dd, J=9, 5.5Hz), 4.02 (1H, dd, J=15.5, 5Hz), 4.07-4.13 (3H, m), 4.18 (1H, t, J=9Hz), 4.89-4.96 (1H, m), 6.89 (1H, d, J=8.5Hz), 6.97 (1H, dd, J=8.5, 2.5Hz), 7.25 (1H, d, J=2.5Hz) IR ν (liq.) cm^{-1}: 1754, 2100 MS (m/z): 393 (M^+) Optical Rotation $[\alpha]_D^{20}$-113.7° (c=0.1, DMSO)
180		Light brown liquid NMR (DMSO-d_6) δ ppm: 2.28 (3H, s), 3.79 (1H, dd, J=9, 5.5Hz), 4.04 (1H, dd, J=15, 5Hz), 4.10 (1H, dd, J=15, 3Hz), 4.19 (1H, t, J=9Hz), 4.90-4.96 (1H, m), 7.20 (2H, d, J=8.5Hz), 7.43 (2H, d, J=8.5Hz) IR ν (liq.) cm^{-1}: 1756, 2096 MS (m/z): 248 (M^+) Optical Rotation $[\alpha]_D^{20}$-178.3° (c=0.1, DMSO)
181		Colorless crystals [iso-Pr_2O] Mp, 54.5~55°C Elemental analysis $C_{12}H_{12}N_2O_2S$ Theoretical C, 58.05; H, 4.87; N, 11.28 Experimental C, 58.13; H, 4.99; N, 11.26 Optical Rotation $[\alpha]_D^{20}$-183.2° (c=0.1, DMSO)
182		Light yellow liquid NMR ($CDCl_3$) δ ppm: 2.33 (3H, s), 3.80 (1H, dd, J=9, 5.5Hz), 3.84 (1H, dd, J=14.5, 3.5Hz), 4.02 (1H, dd, J=14.5, 4.5Hz), 4.08 (1H, t, J=9Hz), 4.80-4.90 (1H, m), 7.20-7.30 (4H, m) IR ν (liq.) cm^{-1}: 1754, 2100 MS MS (m/z): 248 (M^+) Optical Rotation $[\alpha]_D^{20}$-164.4° (c=0.2, MeOH)

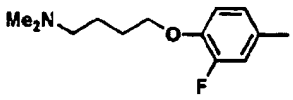
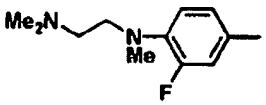
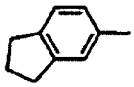
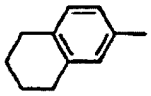


Reference example	R	Form and physical properties [Recrystallization solvent]
183		Colorless prisms [iso-PrOH] mp, 92~92.5°C Elemental analysis $C_{13}H_{14}N_2O_2S$ Theoretical C, 59.52; H, 5.38; N, 10.68 Experimental C, 59.54; H, 5.39; N, 10.65 Optical Rotation $[\alpha]_D^{20}$-175.1° (c=0.1, DMSO)
184		Colorless needles [AcOEt] Mp, 99~100°C Elemental analysis $C_{12}H_{12}N_2O_3S$ Theoretical C, 54.53; H, 4.58, N, 10.60 Experimental C, 54.58; H, 4.66; N, 10.60 Optical Rotation $[\alpha]_D^{20}$-152.6° (c=0.5, MeOH)
185		Colorless needles [iso-PrOH] mp, 62~63°C Elemental analysis $C_{14}H_{16}N_2O_3S$ Theoretical C, 57.52; H, 5.52; N, 9.58 Experimental C, 57.48; H, 5.36: N, 9.51 Optical Rotation $[\alpha]_D^{20}$-153.8° (c=0.1, DMSO)
186		Brown liquid NMR (DMSO-d_6) δ ppm: 0.89 (3H, t, J=7.5Hz), 1.30 (2H, sex, J=7.5Hz), 1.55 (2H, quin, J=7.5Hz), 2.56 (2H, t, J=7.5Hz), 3.79 (1H, dd, J=9, 6Hz), 4.03 (1H, dd, J=15.5, 5.5Hz), 4.11 (1H, dd, J=15.5, 3.5Hz), 4.19 (1H, t, J=9Hz), 7.20 (2H, d, J=8.5Hz), 7.44 (2H, d, J=8.5Hz) IR ν (liq.) cm^{-1}: 1754, 2088 MS (m/z): 290 (M^+) Optical Rotation $[\alpha]_D^{20}$-163.0° (c=0.1, DMSO)



Reference example	R	Form and physical properties [Recrystallization solvent]
187		Light yellow needles NMR (DMSO-d_6) δ ppm: 2.55 (3H, s), 3.89 (1H, dd, J=9.5, 5.5Hz), 4.08 (1H, dd, J=15, 5.5Hz), 4.15 (1H, dd, J=15, 3.5Hz), 4.28 (1H, t, J=9Hz), 4.98-5.03 (1H, m), 7.70 (2H, d, J=9Hz), 8.00 (2H, d, J=9Hz) IR ν (liq.) cm^{-1}: 1748, 2168 MS (m/z): 276 (M^+) Optical Rotation $[\alpha]_D^{20}$-195.6° (c=0.1, DMSO)
188		Light yellow needles [AcOEt] mp, 156~157°C Elemental analysis $C_{17}H_{14}N_2O_3S$ Theoretical C, 62.56, H, 4.32; N, 8.58 Experimental C, 62.49; H, 4.52; N, 8.41 Optical Rotation $[\alpha]_D^{20}$-138.3° (c=0.1, MeOH)
189		Yellow liquid NMR (DMSO-d_6) δ ppm: 3.86 (1H, dd, J=10, 5.5Hz), 4.06 (1H, dd, J=15, 5Hz), 4.14 (1H, dd, J=15, 3Hz), 4.24 (1H, t, J=9Hz), 4.94-5.02 (1H, m), 7.25-7.45 (4H, m), 7.71 (1H, dd, J=13, 2.5Hz), 8.34 (1H, dd, J=5, 1Hz), 8.36 (1H, d, J=2.5Hz) IR ν (liq.) cm^{-1}: 1758, 2092 MS (m/z): 345 (M^+) Optical Rotation $[\alpha]_D^{20}$-104.3° (c=0.1, DMSO)
190		Light yellow prisms [iso-PrOH] Mp, 99.5~100.5°C Elemental analysis $C_{15}H_{18}FN_3O_3S$ Theoretical C, 53.08; H, 5.35; N, 12.38 Experimental C, 53.04; H, 5.27; N, 12.00 Optical Rotation $[\alpha]_D^{20}$-138.5° (c=0.1, DMSO)



Reference example	R	Form and physical properties [Recrystallization solvent]
191		Colorless crystals [AcOEt-iso-Pr_2O] mp, 149~150°C Elemental analysis $C_{17}H_{22}FN_3O_3S$ Theoretical C, 55.57; H, 6.03; N, 11.44 Experimental C, 55.56; H, 6.07; N, 11.49 Optical Rotation $[\alpha]_D^{20}$-38.1° (c=0.1, DMSO)
192		Yellow liquid NMR (DMSO-d_6) δ ppm: 2.13 (6H, s), 2.37 (2H, t, J=7Hz), 2.79 (3H, s), 3.10-3.25 (2H, m), 3.70-4.15 (4H, m), 4.85-4.95 (1H, m), 6.90-7.00 (1H, m), 7.10-7.20 (1H, m), 7.35-7.45 (1H, m) IR ν (liq.) cm^{-1}: 1750 MS (m/z): 352 (M^+) Optical Rotation $[\alpha]_D^{20}$-22.3° (c=0.1, DMSO)
193		Colorless needles [AcOEt] mp, 103.5~104.5 °C Elemental analysis $C_{14}H_{14}N_2O_2S$ Theoretical C, 61.29; H, 5.14; N, 10.21 Experimental C, 61.24; H, 5.13; N, 10.20 Optical Rotation $[\alpha]_D^{20}$-172.7° (c=0.1, DMSO)
194		Colorless needles [iso-PrOH] mp, 122.5~124 °C Elemental analysis $C_{15}H_{16}N_2O_2S$ Theoretical C, 62.48; H, 5.59; N, 9.71 Experimental C, 62.49; H, 5.61; N, 9.65 Optical Rotation $[\alpha]_D^{20}$- 166.8° (c=0.1, DMSO)

Working Example 1: (S)-N-[2-Oxo-3-[4-(thiomorpholin-4-yl)phenyl]oxazolidine-5-yl]methylthiourea

15 mL of a 21% ammonia methanol solution was added to 15 mL of a methanol solution containing 0.76 g of (R)-N-[2-oxo-3-[4-(thiomorpholin-4-yl)phenyl]oxazolidin-5-yl]methylisothiocyanate and the solution was stirred for 19 hours at room temperature. The precipitated crystals were filtered and washed in sequence with water and diisopropyl ether to obtain 0.49 g of colorless crystals. The crystals were recrystallized from an N,N-dimethylformamide-water mixed solution to obtain colorless crystals with a melting point of 194.5~195°C

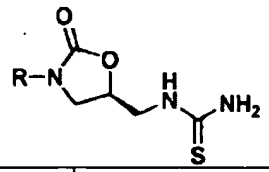
Elemental analysis $C_{15}H_{20}N_4O_2S_2$

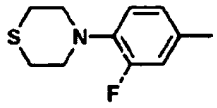
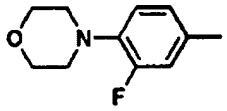
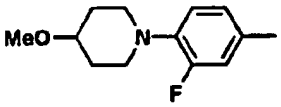
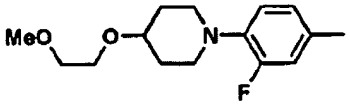
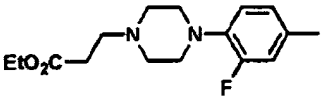
Theoretical: C 51.11; H 5.72; N 15.90

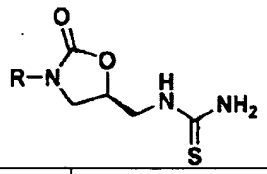
Experimental: C 51.06; H 5.42; N 15.74

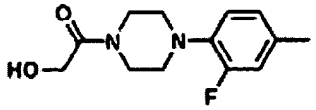
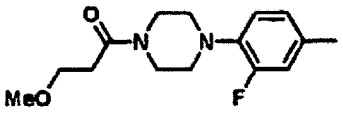
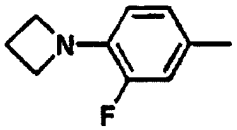
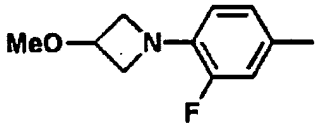
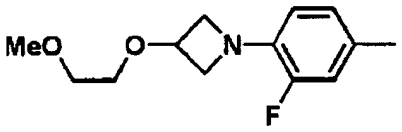
Optical Rotation $[\alpha]_D^{20}$: -19.9° (c=0.1, DMSO)

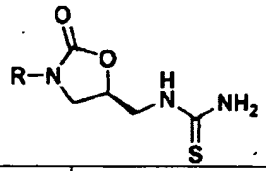
The compounds of Working Examples 2-34 were obtained in the same manner as in Working Example 1.

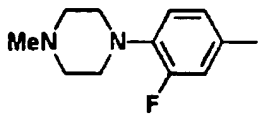
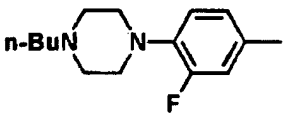
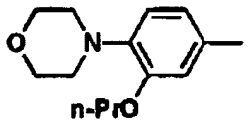
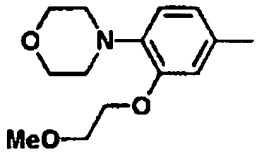
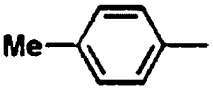


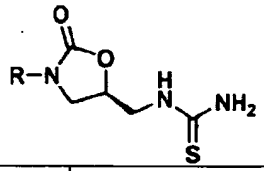
Reference example	R	Form and physical properties [Recrystallization solvent]
2		Colorless needles [CH_3CN] mp, 189.5~190.5°C Elemental analysis $C_{15}H_{19}FN_4O_2S_2$ Theoretical C, 48.63; H, 5.17; N, 15.12 Experimental C, 48.63; H, 5.12; N, 15.05 Optical Rotation $[\alpha]_D^{20}$-16.9° (c=0.1, DMSO)
3		Colorless needles [MeOH] mp, 204~205°C Elemental analysis $C_{15}H_{19}FN_4O_3S$ Theoretical C, 50.84; H, 5.40; N, 15.81 Experimental C, 50.86; H, 5.44; N, 15.88 Optical Rotation $[\alpha]_D^{20}$-19.0° (c=0.1, DMSO)
4		Colorless crystals [EtOH] mp, 169~170.5°C Elemental analysis $C_{17}H_{23}FN_4O_3S$ Theoretical C, 53.39; H, 6.06; N, 14.65 Experimental C, 53.33; H, 6.20; N, 14.62 Optical Rotation $[\alpha]_D^{20}$-16.9° (c=0.1, DMSO)
5		Light brown crystals [AcOEt] mp, 153.5~154.5°C Elemental analysis $C_{19}H_{27}FN_4O_4S$ Theoretical C, 53.51; H, 6.38; N, 13.14 Experimental C, 53.32; H, 6.52; N, 13.06 Optical Rotation $[\alpha]_D^{20}$-17.8° (c=0.1, DMSO)
6		Light yellow crystals [iso-PrOH] mp, 170~171°C Elemental analysis $C_{20}H_{28}FN_5O_4S$ Theoretical C, 52.97; H, 6.22; N, 15.44 Experimental C, 52.98; H, 6.31; N, 15.43 Optical Rotation $[\alpha]_D^{20}$-12.0° (c=0.1, DMSO)

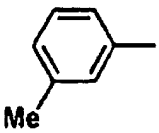
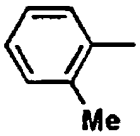
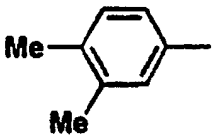
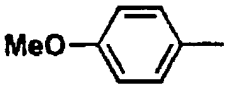


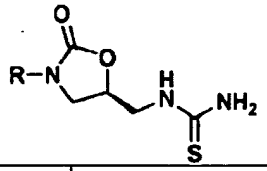
Reference example	R	Form and physical properties [Recrystallization solvent]
7		Light brown crystals [CH_3CN] mp, 199~201°C Elemental analysis $C_{17}H_{22}FN_5O_4S$ Theoretical C, 49.62; H, 5.39; N, 17.02 Experimental C, 49.50; H, 5.66; N, 16.94 Optical Rotation $[\alpha]_D^{20}$-16.1° (c=0.1, DMSO)
8		Colorless prisms [EtOH] mp, 97~99°C Elemental analysis $C_{19}H_{26}FN_5O_4S \cdot 1/4H_2O$ Theoretical C, 51.40; H, 6.02; N, 15.77 Experimental C, 51.19; H, 6.15; N, 15.82 Optical Rotation $[\alpha]_D^{20}$-20.1° (c=0.1, DMSO)
9		Colorless needles [AcOEt] mp, 141~143°C Elemental analysis $C_{14}H_{17}FN_4O_2S \cdot 3/4H_2O$ Theoretical C, 49.77; H, 5.52; N, 16.58 Experimental C, 50.01; H, 5.43; N, 16.34 Optical Rotation $[\alpha]_D^{20}$-15.4° (c=0.1, DMSO)
10		Light brown needles [AcOEt] mp, 133~134.5°C Elemental analysis $C_{15}H_{19}FN_4O_3S$ Theoretical C, 50.84; H, 5.40; N, 15.81 Experimental C, 50.87; H, 5.53; N, 15.55 Optical Rotation $[\alpha]_D^{20}$-15.0° (c=0.1, DMSO)
11		Colorless needles [iso-PrOH] mp, 112~114°C Elemental analysis $C_{17}H_{23}FN_4O_4S \cdot 1/4H_2O$ Theoretical C, 50.67; H, 5.88; N, 13.90 Experimental C, 50.69; H, 5.77; N, 13.93 Optical Rotation $[\alpha]_D^{20}$-15.0° (c=0.1, DMSO)

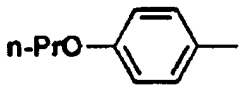
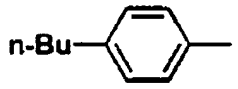
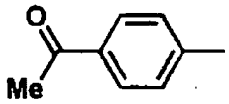
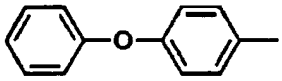
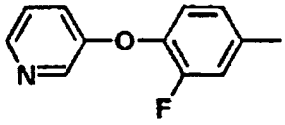


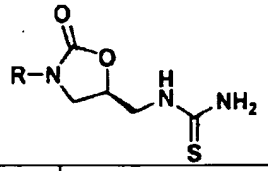
Reference example	R	Form and physical properties [Recrystallization solvent]
12		Light brown prisms [DMF-H_2O] mp, 214~216°C Elemental analysis $C_{16}H_{22}FN_5O_2S$ Theoretical C, 52.30; H, 6.03; N, 19.06 Experimental C, 52.21; H, 6.01; N, 18.82 Optical Rotation $[\alpha]_D^{20}$-26.9° (c=0.1, DMSO)
13		Light yellow crystals [iso-PrOH] mp, 177~178°C Elemental analysis $C_{19}H_{28}FN_5O_2S$ Theoretical C, 55.72; H, 6.89; N, 17.10 Experimental C, 55.60; H, 6.96; N, 17.02 Optical Rotation $[\alpha]_D^{20}$-19.0° (c=0.1, DMSO)
14		Colorless needles [AcOEt] mp, 168.5~170°C Elemental analysis $C_{18}H_{26}N_4O_4S$ Theoretical C, 54.80; H, 6.64; N, 14.20 Experimental C, 54.90; H, 6.36; N, 14.05 Optical Rotation $[\alpha]_D^{20}$-18.0° (c=0.1, DMSO)
15		Colorless needles [EtOH] mp, 159.5~160.5°C Elemental analysis $C_{18}H_{26}N_4O_5S$ Theoretical C, 52.67; H, 6.38; N, 13.65 Experimental C, 52.41; H, 6.50; N, 13.54 Optical Rotation $[\alpha]_D^{20}$-10.0° (c=0.1, DMSO)
16		Colorless needles [MeOH] mp, 140~141°C Elemental analysis $C_{12}H_{15}N_3O_2S$ Theoretical C, 54.32; H, 5.70; N, 15.84 Experimental C, 54.25; H, 5.64; N, 15.70 Optical Rotation $[\alpha]_D^{20}$-12.0° (c=0.1, DMSO)

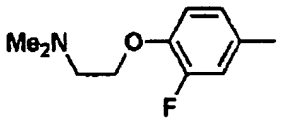
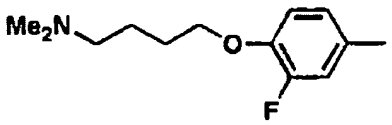
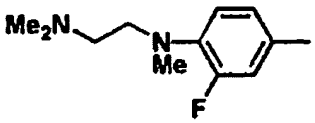
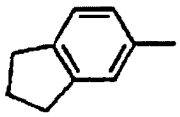
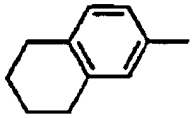


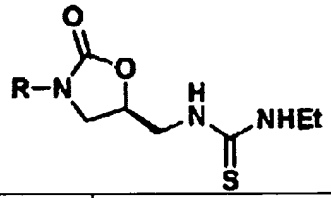
Reference example	R	Form and physical properties [Recrystallization solvent]
17		Colorless prisms [MeOH] mp, 137.5~138.5°C Elemental analysis $C_{12}H_{15}N_3O_2S$ Theoretical C, 54.32; H, 5.70; N, 15.84 Experimental C, 54.21; H, 5.75; N, 15.71 Optical Rotation $[\alpha]_D^{20}$-19.9° (c=0.1, DMSO)
18		Colorless amorphous solid NMR ($CDCl_3$) δ ppm: 2.19 (3H, s), 3.70-3.80 (1H, m), 3.91 (1H, t, J=9Hz), 4.05-4.15 (1H, m), 4.50-4.60 (1H, m), 4.90-5.00 (1H, m), 6.09 (2H, brs), 7.10-7.30 (4H, m), 7.91 (1H, brs) IR ν (liq.) cm^{-1}: 1738 Optical Rotation $[\alpha]_D^{20}$-8.8° (c=0.5, MeOH)
19		Light brown prisms [MeOH] mp, 152~152.5°C Elemental analysis $C_{13}H_{17}N_3O_2S$ Theoretical C, 55.89; H, 6.13; N, 15.04 Experimental C, 55.78; H, 5.97; N, 14.82 Optical Rotation $[\alpha]_D^{20}$-8.0° (c=0.1, DMSO)
20		Colorless prisms [MeOH] mp, 152~153°C Elemental analysis $C_{12}H_{15}N_3O_3S$ Theoretical C, 51.23; H, 5.37; N, 14.94 Experimental C, 51.21; H, 5.35; N, 14.92 Optical Rotation $[\alpha]_D^{20}$-17.4° (c=0.5, DMSO)

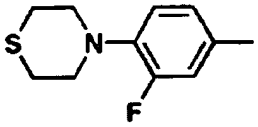
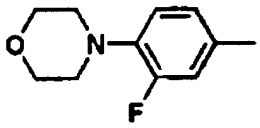


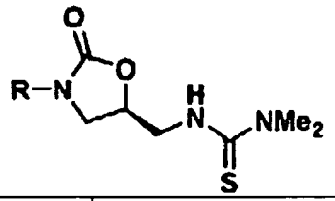
Reference example	R	Form and physical properties [Recrystallization solvent]
21		Colorless needles [AcOEt] mp, 158~160°C Elemental analysis $C_{14}H_{19}N_3O_3S$ Theoretical C, 54.35; H, 6.19; N, 13.58 Experimental C, 54.29; H, 6.39; N, 13.61 Optical Rotation $[\alpha]_D^{20}$-20.0° (c=0.1, DMSO)
22		Colorless crystals [EtOH] mp, 156~158°C Elemental analysis $C_{15}H_{21}N_3O_2S$ Theoretical C, 58.61; H, 6.89; N, 13.67 Experimental C, 58.68; H, 6.76; N, 13.67 Optical Rotation $[\alpha]_D^{20}$-17.9° (c=0.1, DMSO)
23		Colorless crystals [DMF-H_2O] mp, 193.5~194.5°C Elemental analysis $C_{13}H_{15}N_3O_3S$ Theoretical C, 53.23; H, 5.15; N, 14.32 Experimental C, 52.88; H, 5.05; N, 14.05 Optical Rotation $[\alpha]_D^{20}$-20.0° (c=0.1, DMSO)
24		Colorless prisms [MeOH] mp, 173~174°C Elemental analysis $C_{17}H_{17}N_3O_3S$ Theoretical C, 59.46; H, 4.99; N, 12.24 Experimental C, 59.30; H, 5.12; N, 12.03 Optical Rotation $[\alpha]_D^{20}$-9.0° (c=0.2, DMSO)
25		Colorless crystals [AcOEt] mp, 153.5~155°C Elemental analysis $C_{16}H_{15}FN_4O_3S$ Theoretical C, 53.03; H, 4.17; N, 15.46 Experimental C, 53.32; H, 4.24; N, 15.38 Optical Rotation $[\alpha]_D^{20}$-27.0° (c=0.1, DMSO)

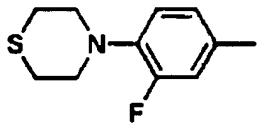
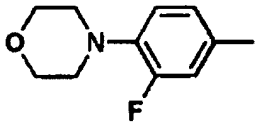


Reference example	R	Form and physical properties [Recrystallization solvent]
26		Light yellow prisms [MeOH] mp, 159~160°C Elemental analysis $C_{15}H_{21}FN_4O_3S$ Theoretical C, 50.55; H, 5.94; N, 15.72 Experimental C, 50.46; H, 5.61; N, 15.33 Optical Rotation $[\alpha]_D^{20}$-14.0° (c=0.1, DMSO)
27		Light brown crystals [MeOH] (Fumarate) mp, 148.5~150°C Elemental analysis $C_{17}H_{25}FN_4O_3S \cdot C_4H_4O_4$ Theoretical C, 50.39; H, 5.84; N, 11.19 Experimental C, 50.23; H, 5.76; N, 11.19 Optical Rotation $[\alpha]_D^{20}$-21.4° (c=0.075, DMSO)
28		Light brown liquid NMR ($CDCl_3$) δ ppm: 2.26 (6H, s), 2.49 (2H, t, J=7.5Hz), 2.85 (3H, s), 3.23 (2H, t, J=7.5Hz), 3.85-3.95 (1H, m), 4.02 (1H, t, J=9Hz), 4.05-4.15 (1H, m), 4.30-4.40 (1H, m), 4.85-4.95 (1H, m), 6.18 (2H, brs), 6.87 (1H, t, J=9Hz), 7.00 (1H, dd, J=9, 2.5Hz), 7.27 (1H, dd, J=14.5, 2.5Hz), 7.55 (1H, brs) IR ν (liq.) cm^{-1}: 1750, 3308 Optical Rotation $[\alpha]_D^{20}$-19.2° (c=0.078, DMSO)
29		Colorless needles [CH_3CN] mp, 144~145.5°C Elemental analysis $C_{14}H_{17}N_3O_2S$ Theoretical C, 57.71; H, 5.88; N, 14.42 Experimental C, 57.51, H, 5.69; N, 14.42 Optical Rotation $[\alpha]_D^{20}$-18.1° (c=0.1, DMSO)
30		Colorless needles [iso-PrOH-iso-Pr_2O] mp, 123~125°C Elemental analysis $C_{15}H_{19}N_3O_2S$ Theoretical C, 58.99; H, 6.27; N, 13.76 Experimental C, 58.96; H, 6.37; N, 13.65 Optical Rotation $[\alpha]_D^{20}$-20.1° (c=0.1, DMSO)



Reference example	R	Form and physical properties [Recrystallization solvent]
31		Colorless needles [CH_3CN] mp, 155~156°C Elemental analysis $C_{17}H_{23}FN_4O_2S_2$ Theoretical C, 51.24; H, 5.82; N, 14.06 Experimental C, 51.22; H, 6.00; N, 14.18 Optical Rotation $[\alpha]_D^{20}$-17.0° (c=0.1, DMSO)
32		Colorless crystals [AcOEt] mp, 166~167°C Elemental analysis $C_{17}H_{23}FN_4O_3S$ Theoretical C, 53.39; H, 6.06; N, 14.65 Experimental C, 53.32; H, 6.03; N, 14.54 Optical Rotation $[\alpha]_D^{20}$-28.0° (c=0.1, DMSO)



Reference example	R	Form and physical properties [Recrystallization solvent]
33		Colorless crystals [EtOH] mp, 145~147°C Elemental analysis $C_{17}H_{23}FN_4O_2S_2$ Theoretical C, 51.24; H, 5.82; N, 14.06 Experimental C, 51.12; H, 5.67; N, 13.89 Optical Rotation $[\alpha]_D^{20}$-23.1° (c=0.1, DMSO)
34		Colorless scales [CH_3CN] mp, 175.5~177.5°C Elemental analysis $C_{17}H_{23}FN_4O_3S$ Theoretical C, 53.39; H, 6.06; N, 14.65 Experimental C, 53.34; H, 5.94; N, 14.58 Optical Rotation $[\alpha]_D^{20}$-24.0° (c=0.1, DMSO)

Working Example 35: (S)-N-[3-[3-fluoro-4-(2-methoxyethoxy)phenyl]-2-oxooxazolidine-5-yl]methylthiourea

0.65 mL of carbon disulfide was added to 15 mL of a toluene solution containing 1.50 g of (S)-5-aminomethyl-3-[3-fluoro-4-(2-methoxyethoxy)phenyl]-2-oxooxazolidine and 0.75 mL of triethylamine while stirring and chilling on ice, and the solution was stirred for 3 h while chilling on ice. 0.55 mL of ethyl chlorocarbonate was added to this mixture, and the solution was stirred for 1.5 hours at the same temperature. Water and 10% sodium hydroxide aqueous solution were added to the reaction solution to render it alkaline, and extraction was performed with ethyl acetate. The extract was washed with saturated sodium chloride aqueous solution, and after drying on anhydrous sodium sulfate, the solvent was evaporated off under reduced pressure. The residue was then washed with diisopropyl ether to obtain 1.45 g of (R)-N-[3-[3-fluoro-4-(2-methoxyethoxy)phenyl]-2-oxooxazolidin-5-yl]methylisothiocyanate as colorless crystals.

42 mL of 16.7% ammonia methanol solution was then added to 14 mL of a methanol solution containing 1.40 g of the resulting colorless crystals while stirring and chilling on ice, and the solution was stirred for 45 h while chilling on ice. The solvent was then evaporated off under reduced pressure, water and 10% sodium hydroxide aqueous solution were added to the residue to render it alkaline, and extraction was performed with ethyl acetate. The extract was then washed with water, and after drying on sodium sulfate, the solvent was evaporated off under reduced pressure. The residue was then purified by column chromatography (alumina, ethyl acetate:n-hexane:methanol = 30:1:1) to obtain 0.52 g of colorless crystals. The crystals were recrystallized from tetrahydrofuran to obtain colorless crystals with a melting point of 137-139°C.

Elemental analysis: $C_{14}H_{18}FN_3O_4S$

Theoretical: C 48.97; H 5.28; N 12.24

Experimental: C 49.20; H 5.13; N 11.97

Optical Rotation $[\alpha]_D^{20}$: -21.0° (c=0.1, DMSO)

The compound of Working Example 36 was obtained in the same manner as in Working Example 35.

Working Example 36: (S)-N-[3-[4-(3-dimethylaminopropoxy)-3-fluorophenyl]-2-oxooxazolidin-5-yl]methylthiourea fumarate

Form: Colorless crystals (recrystallization solvent: MeOH)

Melting point: 149~150°C

Elemental analysis: $C_{16}H_{23}FN_4O_3S \cdot C_4H_4O_4$

Theoretical: C 49.37; H 5.59; N 11.52

Experimental: C 49.47; H 5.70; N 11.27

Optical Rotation $[\alpha]_D^{20}$: -12.0° (c=0.1, DMSO)

Working Example 37: (S)-N-Benzoyl-N'-[3-[3-fluoro-4-(thiomorpholin-4-yl)phenyl]-2-oxooxazolidine-5-yl]methylthiourea

1.20 mL of benzoylisothiocyanate was added to 50 mL of an acetone solution containing 2.44 g of (S)-5-aminomethyl-3-[3-fluoro-4-(thiomorpholin-4-yl)phenyl]-2-oxooxazolidine, and the solution was stirred for 2 hours at room temperature. The reaction solution was concentrated under reduced pressure, and the residue was washed with diethyl ether to obtain 2.16 g of light brown crystals. The crystals were recrystallized from acetonitrile to obtain light yellow crystals with a melting point of 194~195°C.

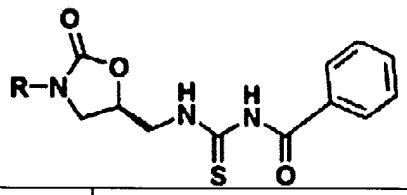
Elemental analysis: $C_{22}H_{23}FN_4O_3S_2$

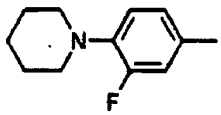
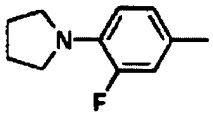
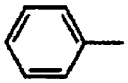
Theoretical: C 55.68; H 4.88; N 11.81

Experimental: C 55.52; H 4.91; N 11.79

Optical Rotation $[\alpha]_D^{20}$: -35.9° (c=0.1, DMSO)

The compounds of Working Examples 38-40 were obtained in the same manner as in Working Example 37.

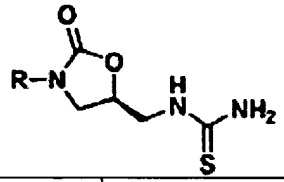


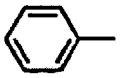
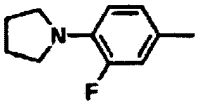
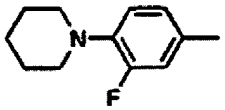
Reference example	R	Form and physical properties [Recrystallization solvent]
38		Light brown crystals [CH_3CN] mp, 163~164°C Elemental analysis $C_{23}H_{25}FN_4O_3S$ Theoretical C, 60.51; H, 5.52; N, 12.27 Experimental C, 60.34; H, 5.59; N, 12.22 Optical Rotation $[\alpha]_D^{20}$-39.1° (c=0.1, DMSO)
39		Light brown crystals [CH_3CN] mp, 202.5~203.5°C Elemental analysis $C_{22}H_{23}FN_4O_3S$ Theoretical C, 59.71; H, 5.24; N, 12.66 Experimental C, 59.70; H, 5.27; N, 12.71 Optical Rotation $[\alpha]_D^{20}$-36.0° (c=0.1, DMSO)
40		Colorless crystals [AcOEt] mp, 141~142°C Elemental analysis $C_{18}H_{17}N_3O_3S$ Theoretical C, 60.83; H, 4.82; N, 11.82 Experimental C, 60.72; H, 4.75; N, 11.80 Optical Rotation $[\alpha]_D^{20}$-46.9° (c=0.1, DMSO)

Working Example 41: (S)-N-[3-[3-Fluoro-4-(thiomorpholin-4-yl)phenyl]-2-oxooxazolidine-5-yl]methylthiourea

30 mL of a methanol solution containing 1.89 g of (S)-N-benzoyl-N'-[3-[3-fluoro-4-(thiomorpholin-4-yl)phenyl]-2-oxooxazolidine-5-yl]methylthiourea and 1.4 mL of 2 N sodium hydroxide aqueous solution was stirred for 1.5 hours at 50°C. After cooling, water was added to the reaction solution and extraction was performed with dichloromethane. The extract was washed with saturated sodium chloride aqueous solution, and after drying on anhydrous sodium sulfate, the solvent was evaporated off under reduced pressure, and the solvent was washed with diisopropyl ether to obtain 1.17 g of light yellow crystals. Colorless needles were obtained by recrystallization from acetonitrile. The product corresponded to the compound obtained in Working Example 2.

The compound of Working Examples 42-44 was obtained in the same manner as in Working Example 41.



Reference example	R	Form and physical properties [Recrystallization solvent]
42		Colorless crystals [AcOEt] mp, 162~163.5°C Elemental analysis $C_{11}H_{13}N_3O_2S$ Theoretical C, 52.57; H, 5.21; N, 16.72 Experimental C, 52.54; H, 5.05; N, 16.57 Optical Rotation $[\alpha]_D^{20}$-16.1° (c=0.1, DMSO)
43		Light brown crystals [CH_3CN] mp, 172~172.5°C Elemental analysis $C_{15}H_{19}FN_4O_2S$ Theoretical C, 53.24; H, 5.66; N, 16.56 Experimental C, 53.38; H, 5.75; N, 16.37 Optical Rotation $[\alpha]_D^{20}$-11.0° (c=0.1, DMSO)
44		Colorless crystals [CH_3CN] mp, 165~166°C Elemental analysis $C_{16}H_{21}FN_4O_2S$ Theoretical C, 54.53; H, 6.01; N, 15.90 Experimental C, 54.32; H, 6.04; N, 15.64 Optical Rotation $[\alpha]_D^{20}$-18.0° (c=0.1, DMSO)

Working Example 45: (S)-N-Methyl-N'-[2-oxo-3-[4-(thiomorpholin-4-yl)phenyl]oxazolidine-5-yl]methylthiourea

0.30 mL of methylisothiocyanate was added to 5 mL of dichloromethane containing 0.50 g of (S)-5-aminomethyl-2-oxo-3-[4-(thiomorpholin-4-yl)phenyl]oxazolidine and 0.55 mL of triethylamine while stirring and chilling on ice, and the solution was stirred for 6 hours at room temperature. Water was added to the reaction solution, and extraction was performed with dichloromethane. The extract was washed with saturated sodium chloride aqueous solution and dried on anhydrous sodium sulfate, before evaporating off the solvent under reduced pressure. The residue was then purified by column chromatography (silica gel, dichloromethane:methanol = 50:1) to obtain 0.50 g of colorless crystals. The crystals were recrystallized from ethyl acetate to obtain colorless crystals with a melting point of 181~182°C.

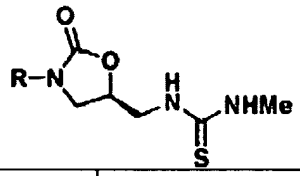
Elemental analysis: $C_{16}H_{22}N_4O_2S_2$

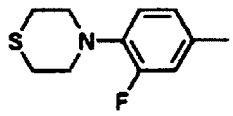
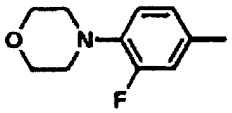
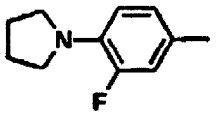
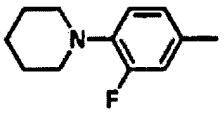
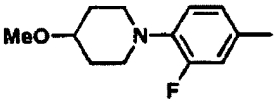
Theoretical: C 52.43; H 6.05; N 15.29

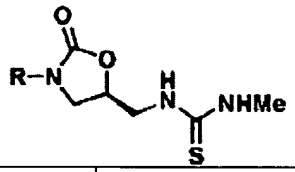
Experimental: C 52.17; H 5.97; N 15.07

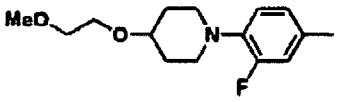
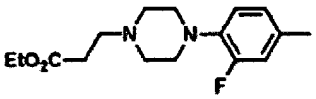
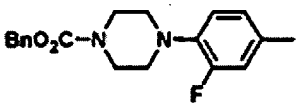
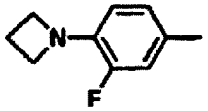
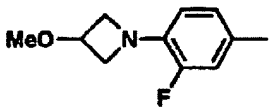
Optical Rotation $[\alpha]_D^{20}$: -19.1° (c=0.1, DMSO)

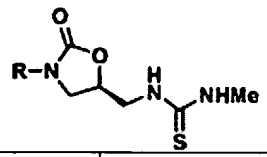
The compounds of Working Examples 46-78 were obtained in the same manner as in Working Example 45.

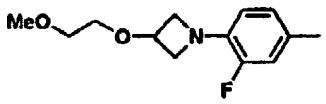
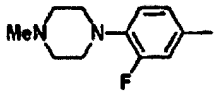
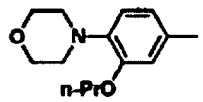
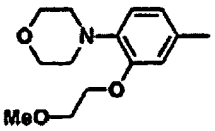


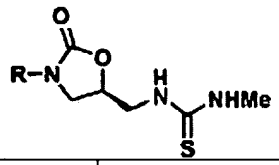
Reference example	R	Form and physical properties [Recrystallization solvent]
46		Colorless cylinders [CH_3CN] mp, 167.5~170°C Elemental analysis $C_{16}H_{21}FN_4O_2S_2$ Theoretical C, 49.98; H, 5.51; N, 14.57 Experimental C, 49.74; H, 5.32; N, 14.47 Optical Rotation $[\alpha]_D^{20}$-21.0° (c=0.1, DMSO)
47		Colorless needles [MeOH] mp, 162~162.5°C Elemental analysis $C_{16}H_{21}FN_4O_3S$ Theoretical C, 52.16; H, 5.75; N, 15.21 Experimental C, 52.21; H, 5.59; N, 15.17 Optical Rotation $[\alpha]_D^{20}$-20.9° (c=0.1, DMSO)
48		Light brown crystals [CH_3CN] mp, 182.5~183.5°C Elemental analysis $C_{16}H_{21}FN_4O_2S$ Theoretical C, 54.53; H, 6.01; N, 15.90 Experimental C, 54.50; H, 6.05; N, 16.08 Optical Rotation $[\alpha]_D^{20}$-19.9° (c=0.1, DMSO)
49		Light yellow prisms [EtOH] mp, 134~134.5°C Elemental analysis $C_{17}H_{23}FN_4O_2S$ Theoretical C, 55.72; H, 6.33; N, 15.29 Experimental C, 55.70; H, 6.40; N, 15.25 Optical Rotation $[\alpha]_D^{20}$-24.0° (c=0.1, DMSO)
50		Colorless needles [AcOEt] mp, 158.5~159.5°C Elemental analysis $C_{18}H_{25}FN_4O_3S$ Theoretical C, 54.53; H, 6.36; N, 14.13 Experimental C, 54.50; H, 6.41; N, 14.01 Optical Rotation $[\alpha]_D^{20}$-16.9° (c=0.1, DMSO)

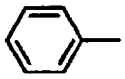
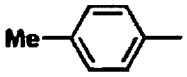
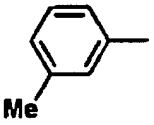
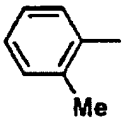


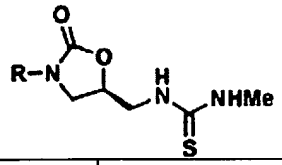
Reference example	R	Form and physical properties [Recrystallization solvent]
51		Colorless needles [AcOEt] mp, 139~140°C Elemental analysis $C_{20}H_{29}FN_4O_4S$ Theoretical C, 54.53; H, 6.64; N, 12.72 Experimental C, 54.26; H, 6.78; N, 12.56 Optical Rotation $[\alpha]_D^{20}$-19.0° (c=0.1, DMSO)
52		Colorless needles [iso-PrOH] mp, 135~137°C Elemental analysis $C_{21}H_{30}FN_5O_4S$ Theoretical C, 53.95; H, 6.47; N, 14.98 Experimental C, 53.73; H, 6.56; N, 14.86 Optical Rotation $[\alpha]_D^{20}$-16.0° (c=0.1, DMSO)
53		Colorless crystals [AcOEt-Et_2O] mp, 123~124°C Elemental analysis $C_{24}H_{28}FN_5O_4S$ Theoretical C, 57.47; H, 5.63; N, 13.96 Experimental C, 57.51; H, 5.67; N, 13.98 Optical Rotation $[\alpha]_D^{20}$-22.0° (c=0.1, DMSO)
54		Colorless needles [AcOEt] mp, 163.5~165.5°C Elemental analysis $C_{15}H_{19}FN_4O_2S$ Theoretical C, 53.24; H, 5.66; N, 16.56 Experimental C, 53.36; H, 5.72; N, 16.22 Optical Rotation $[\alpha]_D^{20}$-17.0° (c=0.1, DMSO)
55		Light brown crystals [iso-PrOH] mp, 137~139°C Elemental analysis $C_{16}H_{21}FN_4O_3S$ Theoretical C, 52.16; H, 5.75; N, 15.21 Experimental C, 52.13; H, 5.59; N, 14.93 Optical Rotation $[\alpha]_D^{20}$-18.1° (c=0.1, DMSO)

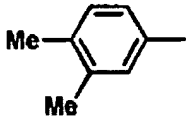
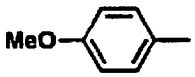
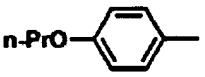
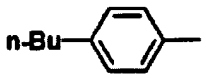


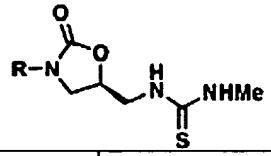
Reference example	R	Form and physical properties [Recrystallization solvent]
56		Light yellow liquid NMR Spectrum (DMSO-d_6) δ ppm: 2.84 (3H, brs), 3.26 (3H, s), 3.45 (2H, t, J=5Hz), 3.53 (2H, t, J=5Hz), 3.60-3.70 (2H, m), 3.75-3.85 (3H, m), 4.05 (1H, t, J=9Hz), 4.05-4.15 (2H, m), 4.35-4.45 (1H, m), 4.75-4.85 (1H, m), 6.50-6.60 (1H, m), 7.10 (1H, dd, J=9, 2.5Hz), 7.37 (1H, dd, J=14.5, 2.5Hz), 7.52 (1H, brs), 7.64 (1H, t, J=5.5Hz) IR ν (liq.) cm^{-1}: 1744, 3328 Optical Rotation $[\alpha]_D^{20}$-20.4° (c=0.1, DMSO)
57		Colorless needles [AcOEt] mp, 153~154.5°C Elemental analysis $C_{17}H_{24}FN_5O_2S$ Theoretical C, 53.53; H, 6.34; N, 18.36 Experimental C, 53.50; H, 6.43; N, 18.32 Optical Rotation $[\alpha]_D^{20}$-25.1° (c=0.1, DMSO)
58		Light brown needles [iso-PrOH] mp, 145~146.5°C Elemental analysis $C_{19}H_{28}N_4O_4S$ Theoretical C, 55.86; H, 6.91; N, 13.71 Experimental C, 55.85; H, 6.83; N, 13.53 Optical Rotation $[\alpha]_D^{20}$-15.0° (c=0.1, DMSO)
59		Colorless crystals [iso-PrOH] mp, 130.5~132.5°C Elemental analysis $C_{19}H_{28}N_4O_5S$ Theoretical C, 53.76; H, 6.65; N, 13.20 Experimental C, 53.56; H, 6.83; N, 13.16 Optical Rotation $[\alpha]_D^{20}$-17.1° (c=0.1, DMSO)

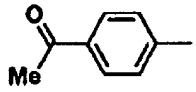
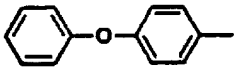
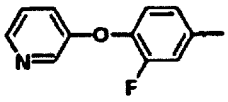
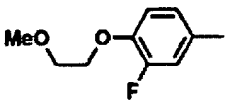


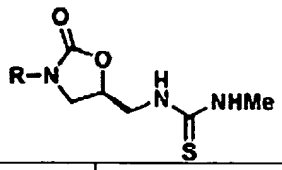
Reference example	R	Form and physical properties [Recrystallization solvent]
60		Colorless needles [THF-iso-Pr_2O] mp, 119.5~121°C Elemental analysis $C_{12}H_{15}N_3O_2S$ Theoretical C, 54.32; H, 5.70; N, 15.84 Experimental C, 54.21; H, 5.57; N, 15.56 Optical Rotation $[\alpha]_D^{20}$-24.0° (c=0.1, DMSO)
61		Colorless needles [AcOEt] mp, 140.5~142°C Elemental analysis $C_{13}H_{17}N_3O_2S$ Theoretical C, 55.89; H, 6.13; N, 15.04 Experimental C, 55.87; H, 6.03; N, 14.88 Optical Rotation $[\alpha]_D^{20}$-17.0° (c=0.1, DMSO)
62		Colorless needles [AcOEt] mp, 126.5~127°C Elemental analysis $C_{13}H_{17}N_3O_2S$ Theoretical C, 55.89; H, 6.13; N, 15.04 Experimental C, 55.89; H, 6.18; N, 14.97 Optical Rotation $[\alpha]_D^{20}$-26.1° (c=0.1, DMSO)
63		Colorless amorphous solid NMR Spectrum (DMSO-d_6) δ ppm: 2.21 (3H, s), 2.87 (3H, s), 3.70-3.83 (2H, m), 3.85-3.95 (1H, m), 3.99 (1H, t, J=8.5Hz), 4.84-4.91 (1H, m), 7.20-7.30 (4H, m), 7.55 (1H, brs), 7.70 (1H, t, J=5.5Hz) IR ν (liq.) cm^{-1}: 1736 MS (m/z): 279 (M^+) Optical Rotation $[\alpha]_D^{20}$-14.5° (c=0.2, MeOH)

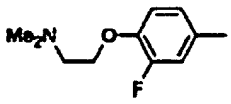
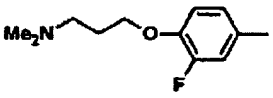
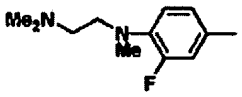
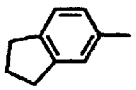


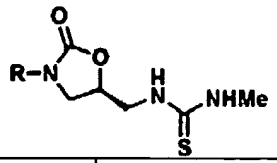
Reference example	R	Form and physical properties [Recrystallization solvent]
64		Colorless prisms [AcOEt] mp, 154~155°C Elemental analysis $C_{14}H_{19}N_3O_2S$ Theoretical C, 57.31; H, 6.53; N, 14.32 Experimental C, 57.15; H, 6.35; N, 14.11 Optical Rotation $[\alpha]_D^{20}$-23.9° (c=0.1, DMSO)
65		Colorless prisms [AcOEt] mp, 114~115°C Elemental analysis $C_{13}H_{17}N_3O_3S$ Theoretical C, 52.86; H, 5.80; N, 14.23 Experimental C, 52.93; H, 5.69; N, 14.17 Optical Rotation $[\alpha]_D^{20}$-24.3° (c=0.5, MeOH)
66		Colorless prisms [AcOEt] mp, 134.5~136.5°C Elemental analysis $C_{15}H_{21}N_3O_3S$ Theoretical C, 55.71; H, 6.54; N, 12.99 Experimental C, 55.47; H, 6.72; N, 12.83 Optical Rotation $[\alpha]_D^{20}$-22.0° (c=0.1, DMSO)
67		Colorless Crystals [iso-PrOH] mp, 110~112°C Elemental analysis $C_{16}H_{23}N_3O_2S$ Theoretical C, 59.78; H, 7.21; N, 13.07 Experimental C, 59.85; H, 7.19; N, 13.04 Optical Rotation $[\alpha]_D^{20}$-19.1° (c=0.1, DMSO)

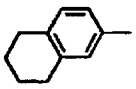
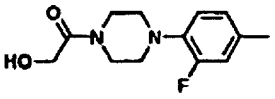
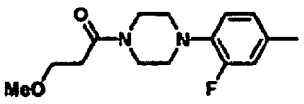


Reference example	R	Form and physical properties [Recrystallization solvent]
68		Light yellow prisms [AcOEt] mp, 157.5~158.5°C Elemental analysis $C_{14}H_{17}N_3O_3S$ Theoretical C, 54.71; H, 5.57; N, 13.67 Experimental C, 54.94; H, 5.52; N, 13.62 Optical Rotation $[\alpha]_D^{20}$-28.9° (c=0.1, DMSO)
69		Colorless amorphous solid NMR Spectrum (DMSO-d_6) δ ppm: 2.84 (3H, s), 3.80-3.90 (3H, m), 4.12 (1H, t, J=9Hz), 4.80-4.90 (1H, m), 6.98 (2H, d, J=7.5Hz), 7.06 (2H, d, J=9Hz), 7.11 (1H, t, J=7.5Hz), 7.36 (1H, d, J=7.5Hz), 7.38 (1H, d, J=7.5Hz), 7.53 (1H, brs), 7.55 (2H, d, J=9Hz), 7.67 (1H, brs) IR ν (KBr.) cm^{-1}: 1738 Optical Rotation $[\alpha]_D^{20}$-17.0° (c=0.2, DMSO)
70		Colorless needles [AcOEt] mp, 153~154°C Elemental analysis $C_{17}H_{17}FN_4O_3S$ Theoretical C, 54.25; H, 4.55; N, 14.88 Experimental C, 54.34; H, 4.58; N, 14.58 Optical Rotation $[\alpha]_D^{20}$-21.0° (c=0.1, DMSO)
71		Colorless crystals [AcOEt] mp, 124.5~125.5°C Elemental analysis $C_{15}H_{20}FN_3O_4S$ Theoretical C, 50.41; H, 5.64; N, 11.76 Experimental C, 50.23; H, 5.77; N, 11.69 Optical Rotation $[\alpha]_D^{20}$-18.9° (c=0.1, DMSO)



Reference example	R	Form and physical properties [Recrystallization solvent]
72		Colorless crystals [AcOEt-Et_2O] mp, 112~113.5°C Elemental analysis $C_{16}H_{23}FN_4O_3S$ Theoretical C, 51.88; H, 6.26; N, 15.12 Experimental C, 51.70; H, 6.20; N, 14.84 Optical Rotation $[\alpha]_D^{20}$-22.0° (c=0.1, DMSO)
73		Colorless crystals [AcOEt-iso-Pr_2O] mp, 96~97°C Elemental analysis $C_{17}H_{25}FN_4O_3S$ Theoretical C, 53.11; H, 6.55; N, 14.57 Experimental C, 52.92; H, 6.41; N, 14.45 Optical Rotation $[\alpha]_D^{20}$-20.0° (c=0.1, DMSO)
74		Yellow liquid NMR Spectrum (DMSO-d_6) δ ppm: 2.18 (6H, s), 2.44 (2H, t, J=6.5Hz), 2.79 (3H, s), 2.85 (3H, s), 3.18 (2H, t, J=6.5Hz), 3.75-3.85 (3H, m), 4.07 (1H, t, J=9Hz), 4.80-4.88 (1H, m), 6.99 (1H, t, J=9Hz), 7.14 (1H, dd, J=9, 2.5Hz), 7.41 (1H, dd, J=15.5, 2.5Hz), 7.52 (1H, brs), 7.65 (1H, t, J=5.5Hz) IR ν (liq.) cm^{-1}: 1750, 3292 Optical Rotation $[\alpha]_D^{20}$-45.7° (c=0.1, DMSO)
75		Colorless needles [AcOEt] mp, 149.5~151°C Elemental analysis $C_{15}H_{19}N_3O_2S$ Theoretical C, 58.99; H, 6.27; N, 13.76 Experimental C, 59.05; H, 6.21; N, 13.71 Optical Rotation $[\alpha]_D^{20}$-26.0° (c=0.1, DMSO)



Reference example	R	Form and physical properties [Recrystallization solvent]
76		Colorless needles [AcOEt] mp, 155.5~160°C Elemental analysis $C_{16}H_{21}N_3O_2S$ Theoretical C, 60.16; H, 6.63; N, 13.16 Experimental C, 60.01; H, 6.84; N, 13.03 Optical Rotation $[\alpha]_D^{20}$-23.1° (c=0.1, DMSO)
77		Colorless needles [EtOH] mp, 188.5~190.5°C Elemental analysis $C_{18}H_{24}FN_5O_4S$ Theoretical C, 50.81; H, 5.69; N, 16.46 Experimental C, 50.70; H, 5.81; N, 16.35 Optical Rotation $[\alpha]_D^{20}$-11.9° (c=0.1, DMSO)
78		Light yellow crystals [AcOEt] mp, 153~155°C Elemental analysis $C_{20}H_{28}FN_5O_4S$ Theoretical C, 52.97; H, 6.22; N, 15.44 Experimental C, 52.75; H, 6.07; N, 15.35 Optical Rotation $[\alpha]_D^{20}$-13.0° (c=0.1, DMSO)

Working Example 79: S-N-[3-[3-Fluoro-4-(piperazin-1-yl)phenyl]-2-oxooxazolidin-5-yl]methyl-N'-methylthiourea

40 mL of 25% hydrogen bromide-acetic acid solution containing 8.30 g of (S)-N-[3-[4-(4-benzyloxycarbonylpiperazin-1-yl)-3-fluorophenyl]-2-oxooxazolidin-5-yl]methyl-N'-methylthiourea was stirred for 30 minutes at 50°C The reaction solution was then concentrated under reduced pressure and the residue was dissolved in dichloromethane before extraction with water. The aqueous layer was then rendered alkaline with 10% sodium hydroxide aqueous solution before extraction with dichloromethane. The extract was washed with saturated sodium chloride aqueous solution, and after drying on anhydrous sodium sulfate, the solvent was evaporated off under reduced pressure. The residue was then purified by column chromatography (alumina, dichloromethane:methanol = 30:1), and the resulting crystals were recrystallized form acetonitrile to obtain 0.50 g of colorless crystals with a melting point of 172.5~174°C.
Elemental analysis: $C_{16}H_{22}FN_5O_2S$
Theoretical: C 52.30; H 6.03; N 19.06
Experimental: C 52.04; H 5.77; N 18.76
Optical Rotation $[\alpha]_D^{20}$: -26.1° (c=0.1, DMSO)

Working Example 80: (S)-N-[3-[4-(4-Benzyloxyacetylpiperazin-1-yl)-3-fluorophenyl]-2-oxooxazolidin-5-yl]methyl-N'-methylthiourea

0.53 mL of benzyloxyacetyl chloride was added dropwise to 50 mL of a dichloromethane solution containing 0.95 g of (S)-N-[3-[3-fluoro-4-(piperazin-1-yl)phenyl]-2-oxooxazolidin-5-yl]methyl-N'-methylthiourea and 0.80 mL of triethylamine while stirring and chilling on ice, and the solution was stirred for 15 minutes while chilling on ice. Water was added to the reaction solution, and extraction was performed with dichloromethane. The extract was washed with saturated sodium chloride aqueous solution, and after drying on anhydrous sodium sulfate, the solvent was evaporated off under reduced pressure. The residue was purified by column chromatography (silica gel, dichloromethane:methanol = 30:1) and the resulting crystals were recrystallized from acetonitrile to obtain 1.0 g of colorless needles with a melting point of 174~175.5°C.
Elemental analysis $C_{25}H_{30}FN_5O_4S$

Theoretical: C 58.24; H 5.86; N 13.58

Experimental: C 58.11; H 5.94; N 13.57

Optical Rotation $[\alpha]_D^{20}$: -10.0° (c=0.07, DMSO)

Working Example 81: (S)-N-[3-[3-Fluoro-4-(thiomorpholin-4-yl)phenyl]-2-oxooxazolidin-5-yl]methyl-N,N'-dimethylthiourea

6.0 mL of a 40% methylamine methanol solution was added to 10 mL of a methanol solution containing 1.0 g of (R)-5-methanesulfonyloxymethyl-2-oxo-3-[4-(thiomorpholin-4-yl)phenyl]oxazolidine and the solution was heated at reflux for 5 days. The reaction solution was then concentrated under reduced pressure to obtain 0.81 g of (S)-3-[3-fluoro-4-(thiomorpholin-4-yl)phenyl]-5-methylaminomethyl-2-oxooxazolidine. 0.70 mL of methylisothiocyanate was added to 16 mL of a dichloromethane solution containing 0.81 g of the resulting crystals and 0.80 mL of triethylamine, and the solution was stirred for 2.5 hours at room temperature. Water was added to the reaction solution and extraction was performed with dichloromethane. The extract was then washed with saturated sodium chloride aqueous solution, and after drying on anhydrous sodium sulfate, the solvent was evaporated off under reduced pressure to obtain light yellow crystals. The crystals were recrystallized form ethanol to obtain 0.50 g of light yellow needles with a melting point of 149~150°C.

Elemental analysis $C_{17}H_{23}FN_4O_2S_2$

Theoretical: C 51.24; H 5.82; N 14.06

Experimental: 51.28; H 5.89; N 13.90

Optical Rotation $[\alpha]_D^{20}$: -12.0° (c=0.1, DMSO)

The compound of Working Example 82 was obtained in the same manner as in Working Example 81.

Working Example 82: (S)-N-[3-[3-Fluoro-4-(morpholin-4-yl)phenyl]-2-oxooxazolidin-5-yl[methyl-N,N'-dimethylthiourea

Form: Colorless prisms (recrystallization solvent: CH_3CN)

Melting point: 167~168.5°C

Elemental analysis: $C_{17}H_{23}FN_4O_3S$

Theoretical: C: 53.39; H 6.06; N 14.65

Experimental: C 53.38; H 5.96; N 14.70

Optical Rotation $[\alpha]_D^{20}$: -28.0° (c=0.1, DMSO)

Working Example 83: (5S)-N-[3-[4-(1-Hydroxyethyl)phenyl]-2-oxooxazolidin-5-yl]methyl-N'-methylthiourea

1 mL of an anhydrous tetrahydrofuran suspension containing 0.70 g of (S)-N-[3-[(4-acetylphenyl)-2-oxooxazolidin-5-yl]methyl-N'-methylthiourea was added dropwise to 15 mL of an anhydrous tetrahydrofuran suspension containing 0.12 g of lithium borohydride, and the solution was stirred for 18 hours at room temperature. Water and 10% hydrochloric acid were added to the reaction solution to render the solution acidic, whereupon extraction was performed with ethyl acetate. The extract was then washed in sequence with water and saturated sodium chloride aqueous solution, and after drying on anhydrous sodium sulfate, the solvent was evaporated off under reduced pressure. The residue was purified by column chromatography (silica gel, dichloromethane:methanol = 30:1) to obtain 0.51 g of colorless amorphous solid.

IR spectrum ν (liq.) cm^{-1}: 1738, 3360

NMR spectrum (DMSO-d_6) δ ppm:

1.31 (3H, d, J=6.5 Hz), 2.84 (3H, d, J=3.5 Hz), 3.75-3.90 (3H, m), 4.10 (1H, t, J=9 Hz), 4.67-4.73 (1H, m), 4.80-4.87 (1H, m), 4.99 (1H, d, J=4.5 Hz), 7.34 (2H, d, J=8.5 Hz), 7.47 (2H, d, J=8.5 Hz), 7.52 (1H, brs), 7.66 (1H, t, J=5.5 Hz)

Optical Rotation $[\alpha]_D^{20}$: -13.6° (c=0.1, DMSO)

Working Example 84: (S)-N-(2-Ethoxycarbonylethyl)-N'-[3-[3-fluoro-4-(thiomorpholin-4-yl)phenyl]-2-oxooxazolidin-5-yl]methylthiourea

5 mL of an acetone suspension containing 0.60 mL of triethylamine and 0.50 g of (S)-N-[3-[3-fluoro-4-(thiomorpholin-4-yl)phenyl]-2-oxooxazolidin-5-yl]methylisothiocyanate was added to 5 mL of water containing 0.22 g of β-alanine hydrochloride while stirring and chilling on ice, and the solution was stirred for 18 hours at room temperature. The precipitated crystals were filtered and washed with ethanol to obtain 0.38 g of colorless crystals, and the crystals were recrystallized from ethanol to obtain colorless prisms with a melting point of 136~137°C.

Elemental analysis: $C_{20}H_{27}FN_4O_4S_2$

Theoretical: C 51.05; H 5.78; N 11.91

Experimental C 51.04; H 5.75; N 11.81

Optical Rotation $[\alpha]_D^{20}$: -24.0° (c=0.1, DMSO)

Working Example 85: (S)-3-[4-[2-Fluoro-4-(2-oxo-5-thioureidomethyloxazolidin-3-yl)phenyl]piperazin-1-yl]propionic acid

8.8 mL of a methanol solution containing 0.44 g of ethyl (S)-3-[4-[2-fluoro-4-(2-oxo-5-thioureidomethyloxazolidin-3-yl)phenyl]piperazin-1-yl]propionate and 0.97 mL of a 2 N sodium hydroxide aqueous solution was stirred for 30 minutes at 60°C. After evaporating off the solvent under reduced pressure, water and hydrochloric acid were added to render the solution acidic. The precipitated crystals were then filtered out and washed with isopropanol to obtain 0.20 g of light yellow crystals. The crystals were recrystallized form ethanol-water mixed solution to obtain colorless crystals with a melting point of 218~220°C.

Elemental analysis: $C_{18}H_{24}FN_5O_4S \cdot 1/4H_2O$

Theoretical: C 50.28; H 5.74; N 16.29

Experimental C 50.37; H 5.76; N 16.32

Optical Rotation $[\alpha]_D^{20}$: -15.9° (c=0.1, DMSO)

The compound of Working Example 86 was obtained in the same manner as in Working Example 85.

Working Example 86: (S)-3-[4-[2-Fluoro-4-[5-(N-methyl)thioureidomethyl-2-oxooxazolidin-3-yl]phenyl]piperazin-1-yl]propionic acid

Form: Colorless crystals (recrystallization solvent: MeOH)

Melting point: 150~152°C

Elemental analysis: $C_{19}H_{26}FN_5O_4S \cdot H_2O$

Theoretical C 49.88; H 6.17; N 15.31

Experimental C 49.69; H 6.39; N 15.47

Optical Rotation $[\alpha]_D^{20}$: -20.1° (c=0.1, DMSO)

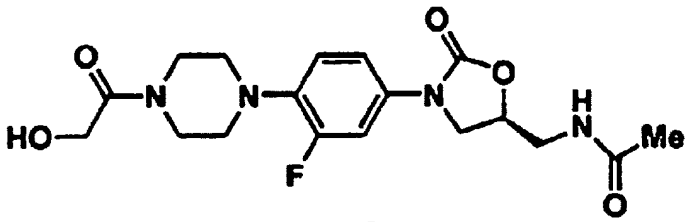
Testing example

In order to confirm the antimicrobial action of the thiourea derivatives of the present invention, antimicrobial testing was carried out with respect to standard strains and clinically isolated strains.

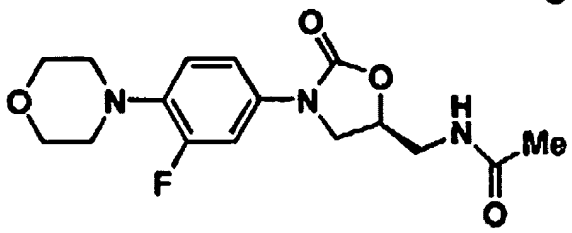
1. Antimicrobial spectrum with respect to standard strains and clinically isolated strains

Standard strains and strains that were isolated from infected individuals (clinically isolated strains) were used, and measurement of antimicrobial power was carried out with a live bacteria count of 10^6 /mL in accordance with the standardized methods of the Japan Chemotherapy Society (*Japan Chemotherapy Society Journal* 29, 76 (1981)). The control compounds were U-100592 and U-100766 (*Journal of Medicinal Chemistry* 39, 673 (1996) and ciprofloxacin (control compounds A, B and C respectively). The results are presented in the table below. The compounds of the present invention exhibited excellent antimicrobial activity with respect to standard strains and clinically isolated strains relative to the comparative compounds. The strains are presented in the table below.

Standard strains:	*Staphylococcus aureus* (*S. aureus*)
	Bacillus subtilis (*B. subtilis*)
Clinically isolated strains:	Methicillin-resistant *Staphylococcus aureus* (MRSA)
	Enterococcus faecalis (*E. faecalis*)



Control compound A
(U-100592)



Control compound B
(U-100766)

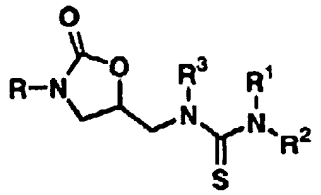
Antimicrobial spectrum with respect to standard strains (minimum inhibitory concentration μg/mL)								
Test strain	Working Examples 2	Working Examples 3	Working Examples 23	Working Examples 35	Working Examples 43	Control compound A	Control compound B	Control compound C
S. aureus FDA 209 JC-1	0.39	0.39	≤0.20	0.78	0.39	0.78	3.13	0.39
S. aureus Terajima	0.39	0.39	≤0.20	0.78	0.39	0.78	3.13	0.39
S. aureus MS 353	0.39	0.78	0.78	1.56	0.39	1.56	3.13	1.56
B. subtilis ATCC 6633	0.20	0.39	≤0.20	0.78	≤0.20	0.78	1.56	0.05
Antimicrobial spectrum with respect to clinically isolated strains (minimum inhibitory concentration μg/mL)								
Test strain	Working Examples 2	Working Examples 3	Working Examples 23	Working Examples 35	Working Examples 43	Control compound A	Control compound B	Control compound C
MRSA HPC 1336	0.78	1.56	1.56	1.56	0.39	3.13	3.13	>100
E. faecalis HPC948	0.39	1.56	1.56	1.56	0.39	3.13	3.13	50
E. faecalis HPC975	0.39	1.56	0.78	1.56	0.39	3.13	3.13	>100

Potential for industrial utilization

The thiourea derivatives and salts thereof of the present invention represented by General Formula (I) exhibit superior antimicrobial action with respect to standard strains as well as clinically isolated strains that include multidrug-resistant bacteria, and are thus extremely useful as antimicrobial agents.

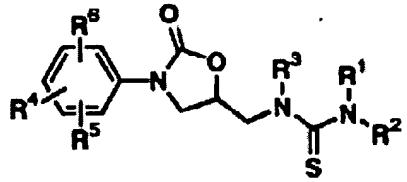
Claims

1. Thiourea derivatives and salts thereof represented by the general formula below:



(in the formula, R^1, R^2 and R^3 each denotes a hydrogen atom, alkyl group, cycloalkyl group, nitrogen atom protective group, alkoxycarbonylalkyl group, substitutable amino group, substitutable aryl group or substitutable benzyl group; and R denotes a substitutable phenyl group).

2. Thiourea derivatives and salts thereof represented by the general formula below:



(in the formula, R^1, R^2 and R^3 each denotes a hydrogen atom, alkyl group, cycloalkyl group, nitrogen atom protective group, alkoxycarbonylalkyl group, substitutable amino group, substitutable aryl group or substitutable benzyl group; R^4, R^5 and R^6 each denotes a hydrogen atom, halogen atom, hydroxyl group, mercapto group, amino group, cyano group, nitro group, carboxyl group, carbamoyl group, substitutable alkyl group, substitutable cycloalkyl group, substitutable alkenyl group, substitutable alkynyl group, substitutable alkoxy group, substitutable alkylthio group, substitutable alkylamino group, substitutable dialkylamino group, substitutable alkylaminocarbonyl group, substitutable dialkylaminocarbonyl group, substitutable alkanoyl group, substitutable halogenoalkanoyl group, substitutable alkanesulfonyl group, substitutable arylcarbonyl group, substitutable aryl group, substitutable aralkyl group, substitutable aryloxy group, substitutable cycloalkyloxy group containing heteroatoms as ring constitutive atoms or substitutable saturated heterocyclic groups; or any two groups of R^4, R^5 and R^6 may form, together with a benzene ring, a substitutable hydrocarbon condensed ring).

3. Drugs containing the compounds according to claim 1 or 2 or physiologically permissible salts thereof as effective components.

4. The drugs according to claim 3, which are antimicrobial agents.

5. The drugs according to claim 3 or 4, having the form of drug compositions that contain formulation additives along with the compounds according to claim 1 or 2 or physiologically permissible salts thereof as effective components.

6. Use of the compounds or physiologically permissible salts thereof according to claims 1 or 2 in the manufacture of the drugs according to any of claims 3-5.

7. A method for treating infections, where said method comprises the administration of a therapeutically effective amount of compound according to claim 1 or 2 or physiologically permissible salt thereof to mammals.

8. The method according to claim 7, wherein the infection is a Gram-positive bacterial infection.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP98/04074

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl[6] C07D263/20, C07D413/10, C07D417/10, A61K31/42, A61K31/425/A61K31/495, A61K31/535
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
Int.Cl[6] C07D263/20, C07D413/10, C07D417/10, A61K31/42, A61K31/425/A61K31/495, A61K31/535

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
REGISTRY (STN), CAPLUS (STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP, 127902, A2 (E.I. DU PONT DE NEMOURS AND COMPANY), 12 December, 1984 (12. 12. 84), (Refer to page 45, Table 3 ; pages 69, 70, Table 7 ; page 72, Table 8 ; page 76, Table 9, Compounds 35, 76) & JP, 60-8277, A	1-6
Y	EP, 789025, A1 (BAYER AG), 13 August, 1997 (13. 08. 97), (Refer to page 17, line 19 to page 19, line 13 ; pages 34 to 41, Table 1) & JP, 9-316073, A & US, 5792765, A	1-6
A	EP, 789026, A1 (BAYER AG), 13 August, 1997 (13. 08. 97), (Refer to pages 25 to 31, Table 1) & JP, 10-1480, A & DE, 19649095, A1	1-6

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 December, 1998 (07. 12. 98)	15 December, 1998 (15. 12. 98)
Name and mailing address of the ISA/ Japanese Patent Office	Authorized officer
Facsimile No.	Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP98/04074

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [x] Claims Nos.: 7-8

because they relate to subject matter not required to be searched by this Authority, namely:

The subject matters of claims 7 and 8 pertain to methods for treatment of the human body by therapy and thus relates to a subject matter which this International Searching Authority is not required, under the provisions of Article 17(2)(a)(i) of the PCT and Rule 39.1(iv) of the Regulations under

2. [ ] Claims Nos.:

because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:

because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

Continuation of Box No. I of continuation of first sheet (1)

the PCT, to search.